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THE SURGICAL CLINICS OF NORTH AMERICA

VOLUME 58 / NUMBER 4
August 1978

SYMPOSIUM ON
BREAST CANCER

Avram M. Cooperman, M.D., and
Caldwell B. Esselstyn, Jr., M.D., *Guest Editors*

W. B. SAUNDERS COMPANY — Philadelphia · London · Toronto

W. B. SAUNDERS COMPANY: West Washington Square
Philadelphia, Pennsylvania 19105

1 St. Anne's Road
Eastbourne, East Sussex BN21 3UN, England

1 Goldthorne Avenue
Toronto, Ontario M8Z 5T9, Canada

The Surgical Clinics are also published in translated editions by the following:

Spanish	Nueva Editorial Interamericana, S.A. de C.V., Cedro 512, Apartado 26370, Mexico 4, D.F., Mexico
Italian	Piccin Editore, Via Porciglia 10, 35100 Padua, Italy
Turkish	Guven Bookstore, Mudafaa Cad. 16–B, P.O. Box 145, Kizilay, Ankara, Turkey
Portuguese	Editora Interamericana do Brazil, Ltda. Av. Venezuela, 131 2. Andar Rio de Janeiro, Brazil
Greek	Mr. Tassos Psaropoulos, Anglo-Hellenic Agency, 5 Koumpari Street, Athens 138, Greece

THE SURGICAL CLINICS OF NORTH AMERICA
August 1978 Volume 58—Number 4

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The following information is published in accordance with the requirements of the United States Postal Code.

The Surgical Clinics of North America is published every other month by W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105, at Hampton Road, Cherry Hill, New Jersey 08002. Subscription price is $30.00 per year. Second-class postage paid at Cherry Hill, New Jersey.

This issue is Volume 58, Number 4.

The editor of this publication is Linda C. Belfus, W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105.

Library of Congress catalog card number 39-19714.

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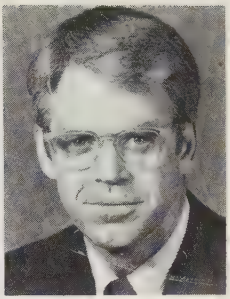

CALDWELL B. ESSELSTYN, JR., M.D.

Foreword

More than 90,000 new primary breast cancers will be detected in 1978. Despite the prevalence of this disease, the issues that plagued surgeons 20 years ago still persist and are largely unresolved.

Emotions are high when discussing mass screening, biopsy, early diagnosis, and what to do with the uninvolved breast. Emotions run even higher when planning treatment for the involved breast and reconstructive surgery. Which type of mastectomy, if any, is optimal and correct, or should we place more emphasis on local excision and irradiation? The role of the pathologist is increasingly important as limited operations are more frequently considered. Added to this has been the revelation that breast cancer may be systemic at the time the primary tumor is diagnosed. Is preoperative radioisotope scanning necessary, and if so what tests should be done (bone scans, liver scans)?

The use of adjuvant chemotherapy has been publicized in several reports. Although much of this information is preliminary, it has been enthusiastically accepted by a hopeful and uncritical public. Castration, adrenalectomy, and hypophysectomy have been practiced for many years, but ofttimes the conclusions are based on limited and uncontrolled studies. Estrogen receptor determination allows more accurate prediction of hormone response. After hormonal manipulation when should this test be done and when should hormonal treatment be used? Immunotherapy and immunology are thought to hold great promise in our understanding and treatment of breast cancer. What is the current state?

These and other issues confront us in our daily surgical practice. In this issue of the *Surgical Clinics* we attempt to answer or review these issues. We were fortunate to have colleagues across this country and continent interested in breast cancer to present their views as objectively as possible.

Our interest in breast cancer first developed of necessity. This necessity was created by the large patient population that our senior colleague, George Crile, Jr., accumulated during a lifetime of interest and practice

in breast disease. His interest and continuous probing have been contagious and stimulating, and his review of these papers is acknowledged and appreciated.

We thank Carol Hoidra, a recent editor, and Linda Belfus, the present editor of the *Surgical Clinics*, for the opportunity to present this material, and Rita Feran who made acceptable English of the manuscripts.

Our greatest debt, empathy, and respect go to our patients with breast cancer (particularly E.M.A.) whose initial joys and subsequent sorrows keep us in search of newer treatments and forever humble.

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Breast Cancer: An Overview

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Depending upon objectivity and experience, surgeons view breast cancer with varying degrees of optimism or pessimism. The divergence of these views is the reason for reappraising the present issues, particularly the curability of this disease. We overview some aspects of breast cancer that are included in this symposium. This article will provide background data.

Early Diagnosis

Many programs have been designed to educate the public about breast cancer and to diagnose smaller tumors at an earlier stage in their development. Although it is believed that breast cancer is frequently incurable at the time of discovery, theoretically there is a time when every cancer is small enough to be treated locally and before it has spread systemically.

Despite intensive public education, the stage of tumor when diagnosed and the survival of the patients have been only slightly altered in the past two to three decades. Most tumors are still detected by patients, not by physicians or xeromammography. Even with the increased awareness of breast cancer and the publicity created by the discovery of breast cancer in the wives of the President and Vice President, there has been little or no change in tumor size or characteristics when contrasted to earlier studies.[3, 9, 21]

The results of mass screening programs have been more encouraging. Strax[33] first reported on a large population screened by physical examination and mammography. Fifty-five cancers were detected, most by clinical examination. The cancers were detected earlier and the death rate was lower when compared with a nonscreened population.

Occult cancers found by xeromammography have fewer nodal metastases and the prognosis has been more favorable. Malone et al.[23] noted that one-third of these cancers were not palpable. Nodal or dis-

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tant metastases were less common than palpable lesions, particularly when a mass lesion without calcifications was shown by xerography. In our unpublished experience, nodal metastases were found in 1 of 4 axillary dissections of nonpalpable cancers discovered by xerography.

The values of screening by xerography and arguments for its use are presented in detail elsewhere in this symposium. Unsuspected breast cancers will be discovered at a rate of 1 to 4 per 1000 examinations. A negative xerogram, if accurate, is no guarantee that a cancer is not present or will not develop. Cancer will develop in some women between screening examinations, sometimes within one month of the last one.[28] Nodal metastases are more common in these women than in women with occult cancers found by screening.[28]

Theoretical considerations against screening are based on the carcinogenic potential of radiation. Whether the risk is less than the benefit depends on the amount of exposure.[15] This is still controversial.

When cancer of the breast is suspected, preoperative screening tests (liver scans, bone surveys) have limited value. Although breast cancer commonly metastasizes to bone, preoperative bone scans in asymptomatic patients with clinical Stage I cancers do not often show evidence of metastases; many of those that are interpreted as showing metastases turn out to be false positives, and are the result of degenerative bone disease. Patients with large Stage I or clinical Stage II breast cancers should have bone scans before mastectomy because in these cases bony metastasis is more common.

Natural History and Curability of Breast Cancer

It is timely to review the natural history of breast cancer as these data provide a basis for comparison with survival curves after treatment. Between 1880 and 1968 four reports on a total of 1617 women recorded the course of untreated breast cancer.[4, 10, 16, 17] Although there was some overlap in patients and some were included in more than one series, three-fourths of the patients had large bulky tumors with metastases to maxillary or supraclavicular nodes. The mean survival was 38 to 40 months. Nine to 20 per cent lived 5 years and 3 to 5 per cent lived 10 years.[4, 10, 16, 17] Obviously, survival was limited in patients with such large and advanced tumors.

Bulky tumors were the rule 50 to 100 years ago, but one would suspect that finding tumors when they were smaller might alter the natural history of untreated breast cancer. MacKay and Sellers[22] reported on 145 untreated cases between 1938 and 1956. One hundred patients with late stage disease and in poor general condition had a mean survival of 3.9 years. Thirty-five per cent were alive at 5 years. Sixty-nine per cent with local disease without evidence of metastases survived 5 years. This high percentage is impressive but may represent a sampling bias or be the result of including many low-grade lesions. This latter fact is important because the prognosis is more favorable for low-grade lesions.

Occasional cases of long-term survivors with untreated breast cancer have been reported. Steckler and Martin[31] reported an unusual

case of a 38 year old woman with biopsy proven (and reviewed) breast cancer who declined surgery and was followed 20 years before consenting to partial mastectomy. Most surgeons have encountered instances in which tumors have existed for years before patients sought or allowed treatment, and the tumors remained confined to the breast often with little change in size. The number of these cases is few and not likely to alter the natural history of the disease.

Biopsy: Timing and Type

Few, if any, surgeons would perform mastectomy without a positive histologic or cytologic diagnosis. There is less agreement on when or what type of biopsy should be done (aspiration, incisional, or excisional). The traditional approach (popularized more than 30 years ago) has utilized incisional or excisional biopsy under general anesthesia, frozen section diagnosis, and immediate mastectomy. The rationale for this approach stemmed from a fear of spreading the cancer by manipulating the tumor, and of increasing the patient's anxiety by two operations. Little or no correlation has been shown between survival and the type of biopsy done or the interval from biopsy to definitive surgery. Today as a result of public education many women have reservations about biopsy and possible immediate mastectomy. Fearing that the pathologist will make a mistake and that the breast might be removed unnecessarily, there is increasing emphasis on outpatient biopsy under local anesthesia. The cost is $300 to $500 less than it is in inpatient procedures under general anesthesia, hospital beds are freed, anxiety is lessened, and there is more time for complete pathologic review and discussion with the patient.[2, 9, 15, 16, 26]

Almost as accurate as a frozen section diagnosis is needle aspiration biopsy, a procedure that is performed in the office using a topical anesthetic and a syringe with an 18 to 20 gauge needle. The success of this technique (described elsewhere) depends on an experienced cytopathologist and accurate sampling of the specimen.[26] An accuracy rate greater than 90 per cent has been attained, and this is our preferred method. In addition to positive cytologic findings, unless there is roentgenographic and clinical evidence of cancer, an open biopsy should be done before the breast is removed. Furthermore a negative cytology does not rule out cancer; it simply means that no cancer cells were included in the specimen.

Surgical Treatment

There is little agreement as to what constitutes adequate treatment for breast cancer. Emotions, satisfaction with a particular method, set habits, and the long time it takes to evaluate newer methods make many surgeons unwilling to modify present operations. Although some surgeons may disagree about the type of mastectomy (radical, extended radical, simple, modified, or partial), others believe that all these operations are too radical and perhaps unnecessary, and that local excision plus curative radiotherapy provide an equal and less mutilating alternative. Proponents of each of these treatment methods express their viewpoints and reasoning in this symposium.

Steinfield[32] dates the history of breast cancer and mastectomy to Galen and Hippocrates. In the United States, Boylston performed a mastectomy on July 28, 1718, and the patient survived for 39 years until the age of 85. The data and event were happily recorded by the patient's husband in an advertisement in the Boston Gazette, November 21, 1720 (a far different type of publicity than today's surgeons receive!).[32]

That surgery rarely cured patients with advanced disease was stated by Paget in 1853:[27] "In deciding for or against the removal of a cancerous breast in any single case, we may, I think, dismiss all hope that the operation will be the final remedy for the disease. I will not say that such a thing is impossible; but it is so highly improbable, that a hope of its occurring in any single case cannot be reasonably entertained." Whether Paget's reflections were on advanced tumors or were a prophecy about the limitations of surgery is not clear.

The classic treatment of primary cancer limited to the breast or axilla is excision of varying amounts of breast tissue and axillary contents. To this has been added radiation therapy, hormonal manipulation, and chemotherapeutic agents.

Certainly the strongest emotions are generated when discussing the role of radical mastectomy. In 1894 Halsted[18] reported on patients treated by en bloc removal of skin, pectoralis major and minor muscle, and axillary dissection. In 1902, 133 operations were reported.[19] At three years, 51 per cent of the patients were living without recurrence; only recurrences in the scar were considered to be local recurrences, but 6 per cent were living with these, and 46 per cent had died of disease. The fact that nearly all lesions involved most of the breast and had skin ulceration or bulky axillary metastases made this method satisfactory to treat these tumors locally. Even then, Rudolph Matas[24] expressed doubts about the operation. His experience with the Halsted mastectomy was less satisfactory, with 62 per cent treatment failures at 3 years.

Although the issues might have been resolved years ago by carefully designed prospective studies, there has been reluctance to submit patients to these trials. It is difficult to accumulate the large numbers of patients necessary to make valid conclusions and there is reluctance to subject patients to these trials for fear of denying them "adequate surgical treatment." Despite this, many questions have been answered by 13 randomized prospective trials in Britain and Ireland comparing different operations and adjuvant therapy.[7] In the United States, Fisher and colleagues[12] have been instrumental in organizing and conducting similar trials. The large numbers of patients included are necessary because of the nonhomogenous clinical behavior of this malignancy. Although the follow-up has been short (less than 10 years in many trials), no operation has proved superior. Stated in other terms, dissimilar operations yield similar results. All operations are reasonably successful in controlling local disease (breast, chest wall, axilla), but the cause of death in most patients is systemic metastases.

There is evidence that too much emphasis has been placed on the

technical aspects of surgical treatment of this disease and until recently the end results and systemic concepts have been ignored.

In 1965, Devitt[11] retrospectively reviewed 922 cases of "curable" breast cancer treated by radical mastectomy or simple mastectomy plus low axillary dissection. Survival rates at 5 and 10 years were similar. Axillary metastases often appeared simultaneously with distant metastases. Devitt concluded that "breast cancer patients do not do poorly because they have regional lymph node metastases but rather they have metastases when they do poorly."

Bond[5] reviewed 16,000 breast cancer cases in Birmingham, England. Of 6775 operable cases, 15 per cent survived 25 years; deaths were due to breast cancer at all years in the follow-up. At 5 years, 80 per cent of deaths were caused by cancer, at 13 years 50 per cent, and at 25 years (when the mean age was 80 years) 20 per cent. The operations done did not influence the end results. Systemic metastases developed in nearly all patients who had local recurrence, usually within 5 years. Radiation therapy appeared to increase the mortality when axillary nodes were not involved at the time of mastectomy.

Adair et al.[1] followed 1458 patients after radical mastectomy for at least 30 years. About 61 per cent died of cancer and 37 per cent were "cured," with 2 per cent lost to follow-up. Cancer developed in the opposite breast in 13 per cent of the survivors. Tumor size and status of axillary lymph nodes correlated with survival. The pivotal figure in this study is the 25 per cent of patients who died of other causes.

Brinkley and Haybittle[6] followed 704 women with breast cancer 20 or more years after treatment. Eighteen per cent of all patients and 30 per cent of patients with Stages I and II cancer could be considered cured, as their survival curves paralleled the normal population after 22 years. Even then the death rate from cancer was much higher than anticipated. After 20 years 8 of 23 died of cancer. In one-fourth of the long-term survivors, the axillary nodes were involved.

In the United States, Mueller and Jeffries[25] followed 1513 women treated for breast cancer for 15 or more years. The influence of treatment, early diagnoses, staging, patient's age, and histologic characteristics of the lesion were not considered. Eighty to 85 per cent died of breast cancer during the period of the study. Although frequently older patients died of other illnesses, the annual death rate from breast cancer was steady at 8 per cent per year. Again, this substantiates the view that the longer breast cancer patients are followed, the higher the death rate from cancer.

Cell Kinetics

Disappointing results of treatment of breast cancer have led to the suggestion that tumor cells have metastasized long before the discovery of the primary tumor. Cell kinetics and doubling times in experimental and human studies support this. (Malignant tumors exist long before cancers are discovered, at a time when treatment would be more effective.) The present concept is that a single mutant tumor cell repeatedly divides, as do its descendants, thereby establishing them-

selves as a colony. After a certain number of divisions, the neoplasm attains such a size that it can be discovered by roentgenographic or physical diagnosis. Although growth rates of tumor cells are related to time, size, and environmental factors (including nutrition and resistance), these cannot be measured and their importance is unknown. For example, a 10 micron cancer cell becomes 1 mm (10^6) in 20 doublings and 1 cm in 30 doublings (10^9 cells).[20] In one series, 20 per cent of patients with 1 cm tumors had axillary metastases.[13] Although 1 cm is generally stated to be the smallest size at which tumors are often detected clinically, detection depends greatly on the location of the tumor in the breast and the amount of surrounding mastitis. If 1 cm is the smallest size for clinical detection and one-fifth of patients with tumors of this size die of metastases within 8 years, there is good cause for frustration and disappointment with the present treatment of breast cancer.

Some methods used to estimate doubling times of breast cancer include measurements of primary tumors and pulmonary and cutaneous metastases.[8, 14, 20, 30] Gershon-Cohen et al.[14] measured doubling times by mammography. Times ranged from 23 to 209 days. Tumor cells could have been present from 2 to 17 years before discovery.[14] They noted that patients with axillary metastases (eight patients) had doubling times averaging 85 days; doubling times for those without metastases (10 patients) averaged 128 days. In another study, there was a direct relation between tumor doubling time and postoperative survival in that the survival curve for rapidly growing tumors descended steeply for 5 years after primary treatment (70 per cent had died by then).[20]

On the basis of these types of studies, breast cancer cells have been classified as slow growing (doubling time more than 150 days), moderately fast growing (75 to 150 days), and fast growing (less than 75 days).[14] In some patients, breast cancers of microscopic size have spread systemically at the time they are discovered.

Despite the roentgenographic evidence cited above, there are problems. Tumors are complex structures with both proliferating and nonproliferating parts, areas of regression, necrosis, hemorrhage, and maturation or dedifferentiation — factors not taken into account by roentgenographic measurements. Therefore judging the age and size of a tumor by doubling times may give false estimates. Also it is possible that the "sudden appearance" of metastatic cells represents a failure of host resistance, which had kept dormant tumor cells in check until the balance shifted. Circulating tumor cells may or may not implant and grow. Thus host factors, presently undefined, influence both implantation and growth.

Personal Perspective

Unfortunately, carcinoma confined to the breast or breast and axilla has been the subject of most surgical reports. Systemic and distant metastases, beginning as microscopic foci initially undetected, are beyond the scope of local treatment and cause death in most patients.

If these metastases could be diagnosed before surgery, treatment could be modified. To control systemic disease, one or more measurements including hormonal manipulation (based on estrogen receptor studies), chemotherapy (based on numbers of involved lymph nodes and menopausal status), and perhaps immunotherapy can be used. These subjects are covered elsewhere in this symposium.

Our role as surgeons is to treat the local and regional disease. By processes that will accurately stage a tumor and permit biological assessment, it should become possible to treat smaller localized tumors by partial mastectomy or excision and radiation therapy. For multicentric tumors, total mastectomy can be utilized. In patients with regional nodal involvement, excision (by partial or total mastectomy) plus axillary dissection or radiation may be employed with equal success. In the unusual case of a large apparently localized tumor, mastectomy plus excision of part or all of the underlying muscles may occasionally be necessary.

Newer and more encouraging results with systemic chemotherapy should be received with cautious enthusiasm pending longer evaluation and follow-up.

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Evaluation of Screening Programs for the Early Diagnosis of Breast Cancer

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There is an increasing awareness among cancer investigators that breast cancer may be a systemic disease from its inception. There is also increasing evidence that its initial clinical manifestation in the vast majority of cases is a localized lesion in one breast, although there may be evidence of microscopic totally occult dissemination elsewhere. At the same time it is generally agreed that the immunologic system can, and usually does, cope with this type of dissemination, particularly if the clinical tumor burden is removed.

The secret of success in the treatment of breast cancer may lie in the stage at which intervention is introduced. If breast cancer is found and treated when localized, and the disease can be completely removed at a time when immunocompetence is intact, the cure rate is high. When we consider that the cause of breast cancer and possible primary prevention still elude us and that our present forms of treatment are mainly effective when dealing with localized disease, the value of early detection becomes obvious. The important question today is how can we make such detection practical, efficient, and economical.

RATIONALE

The concept of mass screening for early detection of breast cancer is based on three points:

1. The seriousness of the problem of breast cancer in American women:

• The breast is the most common site of cancer in women, constituting 28 per cent of all cancer in women. One of every 13 females in this country develops the disease in her lifetime. About 90,000 cases are diagnosed every year.

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Supported in part by National Cancer Institute Contract 1-CN-35004.

• Breast cancer is the most common cause of death in women aged 39 to 44. Every 15 minutes a woman dies of breast cancer, with some 34,000 deaths per year.

• The incidence of breast cancer increases with age. A woman at 70 has six times the chance of harboring a breast malignancy as has a woman at 40. The incidence of breast cancer has been increasing by 1 per cent per year for at least the last 10 years. A particularly steep rise has occurred in women under 40.

• About one-third of cases of breast cancer are presented to the physician in a stage too advanced to enable possible cure. It has been estimated that in this country today not more than one-fourth of women with breast cancer are alive and free of disease 10 years after diagnosis.

• The death rate from breast cancer has been stationary over the past 40 years in spite of advances in surgical, radiotherapeutic, and chemotherapeutic techniques.

2. We know that:

• We cannot prevent breast cancer. We can prevent death from breast cancer if the cancer is detected at an earlier stage than is usual in general medical practice. This involves examining a woman before she would ordinarily bring her problem to her physician, often before she is even aware that a problem exists. The only way to accomplish such early detection is through screening.

• Over 90 per cent of breast cancer is detected initally by the woman herself. The vast majority of women have not learned self-examination of the breasts. The discovery of the disease is accidental and, apparently, too late. Most breast cancer seen by the physician is late cancer with definite nodal involvement.

3. The results of the mass screening program for breast cancer of the Health Insurance Plan of Greater New York continue to show a persistent one-third reduction in mortality in a study group of 31,000 randomly selected women aged 40 to 64 versus a matched control group. In a nine year period of follow-up of breast cancer found within 5 years of diagnosis, 128 deaths from breast cancer occurred in the control group compared with 91 in the study group, only two-thirds of whom had actually been examined. These statistics refer to actual saving of lives, not just increased survival, and serve as a rational basis for the use of mass screening for breast cancer as a means of reducing mortality from this disease.

As defined by the World Health Organization, screening is "the presumptive identification of unrecognized disease or defect by the application of tests, examination or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment." It should be noted that by definition, unrecognized symptomatic as well as presymptomatic disease is included. Tests may be diagnostic, though not necessarily so intended. Thus

mammography or palpation is covered by this definition, provided it is rapidly carried out.

The object of screening for breast cancer is to discover those among the apparently well who have the disease. The disease involved should stand a reasonable chance of being cured if detected early, whereas if not diagnosed until the patient comes to the physician with clear cut symptoms, may be incurable.

A definite diagnosis of breast cancer or benign disease is made only by the pathologist with his microscope. The clinician or radiologist only expresses a suspicion of the presence of breast cancer. The step preceding suspicion is detection of an abnormality. Occasionally, a physician will detect an unsuspected breast condition in the course of an examination unrelated to the breast. However, over 90 per cent of the time, detection is by the woman herself on the basis of a mass, change in appearance, localized pain, or discharge from the nipple. That is why self-examination of the breasts has been, is, and probably always will be a vital step in the diagnosis of breast cancer.

METHODS OF SCREENING

The three important methods used in screening for breast cancer are clinical examination, including palpation and inspection, mammography, and thermography.

Clinical Examination

This time-honored method has been used alone as a screening technique for many years by many cancer authorities such as Holleb[4] and Day and Venet[3] in New York and Gilbertsen[8] in Minneapolis who indicated that detection of early breast cancer would result in improved survival. They also properly felt that screening of apparently well women could lead to finding cancer in more curable stages. A series of reports by these authors showed that periodic examination would detect a higher percentage of cancers without axillary nodal involvement. Gilbertsen and Kfelsberg found remarkable improvement in 5 and 10 year survival results in a group of women followed annually with palpation and inspection. Their results were presented at a time when mammography was not in common use, so that only palpation and inspection were used. Also, the studies listed a disturbingly high percentage (about 30 per cent) of cancer found in an "interval" stage, i.e., within a year of a supposedly negative examination. We now know that a substantial proportion of such cancers was probably detectable by mammography, if not by clinical examination, at the time of the screening study.

Clinical examination is an essential feature in screening for breast cancer. However, it is particularly difficult to locate by palpation the presumably early and small cancers, which often have characteristics associated with benign lesions. The clinician must be aware of this potential pitfall, which is particularly great in large-breasted, postmenopausal women. Mammography will detect a substantial number of cancers that

are not palpable, but many cancers that are palpable are not detectable with present mammographic techniques; therefore, if a clinical examination indicates a possible lesion, a negative mammogram must never deter the clinician from exploration. The value of palpation in screening is directly related to the expertise of the examiner. All physicians involved in screening should assiduously cultivate the art of clinical examination, which may be the sole indicator of cancer in a curable stage.[20]

Mammography

The female breast is readily accessible to inspection and palpation. Why then do we need mammography?[17]

The breast is normally a multinodular structure generally made up of various sized small or large "lumps." The dominant mass that suggests a disease state may not be clearly evident on inspection or palpation, particularly in early cancer. The mammogram is the most useful modality that very often gives the physician that extra assurance that he may be dealing with a malignant or benign process. It is often the added bit of suspicion that leads to prompt exploration.

In the face of a definite lesion on clinical examination that is about to be explored, the mammogram can yield additional information about the rest of the breast or the opposite breast. A cancer that is completely nonpalpable may be lurking elsewhere in either breast, and that "other" lesion and not the mass leading to exploration may be the cancer.

One of the most cogent reasons for mammography, particularly in the symptomatic woman who feels a vague mass or has severe localized pain or nipple discharge, is the varied expertise of physicians in clinical examination of the breast. Mammography may be particularly valuable to the average physician, with average experience in breast palpation, when confronted with a breast problem. A mammogram can be life-saving in avoiding delay, especially in the doubtful case.

It has been known for many years that breast cancer may not be palpable by even the most expert hands. Mammography and clinical examination, which have been used for about 15 years, have detected hundreds of such lesions. Nonpalpable cancers, usually without nodal involvement and accompanied by a substantially increased survival and often reduction in mortality, have brought the importance of x-ray examination of the breast to the fore.

Mammography can detect nonpalpable cancer when it is still localized and probably curable in three ways: by finding a dense mass that is too small in proportion to the size of the breast to be felt; by detecting the microcalcifications of intraductal carcinoma, often noninvasive, before a mass has developed; or by detecting the trabecular distortion of a cancer before the fibroblastic response which makes it palpable has developed.

In the early and mid 1960's Gershon-Cohen et al.,[7] Stevens and Weigen,[16] and Friedman et al.[6] discussed the use of mammography as a screening procedure for breast cancer with mixed results. All reported detecting occult, nonpalpable cancer, especially on periodic study. Their conclusions varied from enthusiastic acceptance to mild approv-

al for women over the age of 50. Most believed that the cost and effort of mass screening were too great for the resultant benefit.

These studies suffered from a lack of a combined approach using both clinical examination and mammography and from absence of a control group for true evaluation of the potential of mass screening in reduction of mortality. The study of the Health Insurance Plan involved large numbers of women and contained a built-in matched control group. Its data strongly indicated that mass screening could save lives. The x-ray study was a major factor in this reduction. Of 44 cases detected by mammography alone and not felt on clinical examination, only 3 women have died in 9 years.

The value of film mammography has been enhanced in recent years by improved radiographic equipment especially designed for this purpose. Such improvements include molybdenum anode tubes and compression which increase the contrast of breast soft tissue with improved accuracy of interpretation.

The importance of mammography versus clinical examination varies with the type of breast, the stage of the cancer, and the type of patient. For example, in the small glandular breast, the large cancer mass, and in premenopausal women, clinical examination is more efficient. In the large fatty breast, as in older women, in the small cancer mass, or cancer without a mass, the x-ray examination may be more informative.

An important principle in breast cancer therapy needs to be emphasized. Because neither palpation nor mammography is 100 per cent accurate, if a cancer is supected on palpation, a negative mammogram should never be allowed to delay exploration of a breast. Similarly, a clinician who is faced with negative clinical findings, but with a positive mammographic report, should seriously consider exploration. The two modalities are truly complementary and should never be considered to be competitive.

Xeromammography[22] is merely a variation of mammography in which the same x-ray films are used to produce the image. A charged selenium plate is used instead of film and the end result is a mammographic image on paper with considerable edge enhancement. There is a difference of opinion among radiologists as to the superiority of the two display mediums. Most experienced mammographers think that the microcalcifications may be more easily detected on the xerox plate but that masses are more easily detected on the improved film mammography. The advantages and limitations of film mammography apply to xeromammography as well.

Radiation Dosage. Recent years have seen a dramatic improvement both in the quality of mammography and in the dosage of radiation used. The most widely used technique in the 1960's, purporting to produce the highest quality, was that of Egan,[4] involving a slow industrial Kodak type M film, a tungsten tube, close coning, no compression with low kilovoltage and high milliampere seconds. This technique produced high quality mammograms with radiation doses ranging from 7 to 12 R to the skin per examination. In the last few years, under the leadership of British radiologists such as Price et al.[14] and Ostrum et al.,[13] and others in this country, the use of faster film-screen

combinations in vacuum cassettes has led to remarkable improvement in contrast and resolution of the mammographic image plus a reduction in radiation to levels of 0.2 to 0.3 R to the skin. The latest measurements by Miller and associates[11] indicate that such skin radiation, with low kilovoltages and the molybdenum anode tubes and compression techniques, is delivering doses to the mid breast of .02 to .03 rads for a right angle pair of films. These techniques are readily available and are being used by an increasing number of radiologists. Revision of techniques in xeromammography with the introduction of the negative mode and increase of kilovoltage has resulted in reduction of radiation, though not to the low levels attainable by the newer film-screen techniques. Wilkinson and associates[21] have produced high quality mammograms with Xerg (Xonics) techniques with markedly reduced radiation to levels even lower than the best of the film-screen techniques. This process holds great promise for the development of mammography techniques with radiation dosage so low as to be negligible considering the potential benefit of the x-ray study of the breast.

Thermography

Thermography is useful in the diagnosis of breast cancer in a more peripheral manner. It detects physiologic changes resulting in increased heat measured by special heat sensors and translated into a photographic image. Many breast conditions, both benign and malignant, are associated with increased heat. Thermography is thus not an indicator of cancer as such; however it does alert the clinician to the possibility of the disease. Areas of increased heat do not necessarily correspond to the location of the cancer, however, and thus exploration cannot be performed on the basis of an abnormal thermogram alone. Clinical examination or mammography is needed for more definite diagnosis and localization. It can be of great help in the case that is otherwise doubtful. A hot thermogram will tend to encourage exploration and thus avoid missing an early case. Approximately 20 to 25 per cent of abnormal thermograms are found in those with no abnormal findings from other methods. These need to be watched more closely and may represent a high risk group. Some observers have found occasional cancers becoming apparent clinically one to two years after positive thermograms.[5, 10, 12]

In the diagnosis of breast cancer, thermography should never be used alone, even as a prescreener. It is particularly ineffective in detecting the very early nonpalpable cancer. It may be of value as an ancillary method for detection of breast abnormalities particularly in tandem with clinical examination and mammography.

A recent joint statement by the American College of Radiology and the American Thermographic Society defines thermography as a "complementary diagnostic tool that may be useful in evaluation of breast disease when combined with both physical examination under the supervision of a qualified physician and mammography by a trained radiologist."

Self-Examination of the Breasts

Unfortunately, some cancers still elude present methods of detection. Some 10 per cent of cancers will become apparent within a year of a negative examination, and reliance is placed on self-examination of the breasts to detect these. At the time of clinical examination, every woman should be educated and encouraged to use self-examination.

One of the major benefits of mass screening is the opportunity it presents to indoctrinate large numbers of women to use self-examination. Gallup polls indicate that a high percentage of women who have been taught self-examination of the breasts by a medical or trained paramedical person respond with long-term, regular self-examination. What is needed is the widespread realization by the medical profession that a pamphlet or a movie is not enough. A woman must be taught self-examination by using her own hand on her breasts under the direct guidance of a professional person.

RISK FACTORS

Women in general are at varying risk of developing breast cancer. Age, of course, is a most important factor. Breast cancer is uncommon in women under 35 years. Other risk factors include: presence of a dominant lump, localized pain, or nipple discharge (many authorities include "chronic mastitis" with or without pain);[2] history of previous breast cancer; positive family history, especially of premenopausal breast cancer; no children or birth of a first child after the age of 30; early menarche (before age 11) or late menopause; and less well known factors such as being Jewish of European extraction, being in the middle or upper income brackets, or postmenopausal obesity. In any large series of breast cancers, especially those detected under screening auspices, the vast majority of malignancies are found in women who have none of the risk factors listed above, with the exception, perhaps, of minor symptoms. However, the presence of any of the above factors increases the need for periodic surveillance.

RESULTS

Health Insurance Plan Study

In this study, 62,000 women aged 40 to 64 were randomly selected as 31,000 pairs, carefully matched, and divided into a control group and a study group. The study group, two-thirds of whom responded, were invited to undergo examinations, which consisted of palpation and mammography, independently. Examinations were carried out initially and in three annual studies. Since that time, data have been collected.

As noted above, there has been a persistent one-third reduction in

mortality in a nine year period of follow-up. The role of mammography was emphasized in this study in which all those examined underwent independent mammography as well as clinical examination. Of all the cancers detected through screening in this study, one-third were found on mammography alone and were not felt by palpation. However, it should also be emphasized that two-fifths of the cancers were found on clinical examination alone and were not detected by x-ray films. Obviously, both modalities were necessary for proper yield. A high percentage of cancers detected by one modality alone demonstrated no axillary nodal involvement — 79 per cent in those found on mammography alone and 75 per cent in those detected by clinical examination alone. It appears that in early breast cancer only one modality may be positive in a high percentage of cases. Cancers found on both modalities had the same percentage of positive nodes (over 50 per cent) as did the control group.

Another important finding was that 15 per cent of the cancers found in the study developed within 12 months after an apparently negative examination, so-called "interval" cancers. These cancers had the same percentage of nodal involvement as did the control group. In subsequent screening programs, this factor needed further attention.

The entire reduction in mortality was concentrated in women over the age of 50; those under 50 showed no improvement. Mammography is less effective in younger women when the breasts are more glandular and more dense on mammograms.[15, 18]

Guttman Institute Study

The above considerations led to the development in 1968 of the Guttman Breast Diagnostic Institute in New York City with the basic objective of developing a mass screening approach that would be feasible and could reach the general population of women.

Of 162,876 examinations made between 1971 and 1975, 61,994 were initial studies and 64,478 were subsequent examinations. Of 4501 recommendations for biopsy or aspiration, 2815 were done and 641 cancers were found.

On initial examination, the proportion of prevalent cancers present was high (8.4 cancers per thousand), depending on such factors as self-selection and age of women. Because cancers had been present for varying lengths of time, only 48 per cent of the cancers were free of nodal involvement. On subsequent examination, the proportion of incident cancers that had become detectable since the previous examination was 2.5 per 1000, but 74 per cent had no nodal spread. Use of clinical examination supplemented by mammography and thermography showed that 20 per cent of the cancers were found by mammography alone, 22 per cent by clinical examination alone, and 58 per cent by a combination of both.

As in the Health Insurance Plan study, 70 per cent of cancers found by mammography alone had no nodal involvement, as did 65 per cent of those found by palpation alone, whereas 44 per cent of cancers found by a combination of both methods had negative nodes.

The importance of teaching self-examination of the breasts is emphasized by the finding of 9 per cent interval cancers, with two-thirds of them having no nodal involvement.[19]

Breast Cancer Detection Demonstration Projects

With the Guttman Institute as a prototype, 26 other screening projects, involving 28 other centers, have been funded by the National Cancer Institute and the American Cancer Society. About 280,000 women have been involved in this program. The objectives of this program were to demonstrate whether women could be motivated to accept screening and whether substantial numbers of breast cancers could be found in a localized, potentially curable stage. Both objectives have been fulfilled. The allotted numbers of screenees were rapidly filled in all centers and substantial numbers of early cancers found. Mammography has been found to be particularly effective in detecting early and even minimal cancers. As of early 1977, 2379 cancers had been found. Of these, 44 per cent were detected on mammography and were not palpable, with 77 per cent without nodal involvement. Also, 40 per cent of the cancers were found in women under age 50 and in 73 per cent there was no nodal involvement. Women over age 50 had 60 per cent of the cancers with 79 per cent without nodal involvement. Figures comparable to the Health Insurance Plan data were 33 per cent of cancers were found on x-ray alone with 79 per cent without nodal involvement; 23 per cent of the cancers were in women under age 50 with 68 per cent without nodal involvement. Also 77 per cent of the cancers were in women under 50 with 76 per cent without nodal involvement. Even more important, in the Health Insurance Plan study, 3.5 per cent of the cancers found were under 1 cm in size with none of these found on mammography alone. In these screening projects, findings included 13.8 per cent of cancers under 1 cm in size, with 58.6 per cent of these found on the x-ray alone.

Apparently, the improved mammographic techniques used in the new studies have resulted in a substantial increase in cancers found on mammography alone, especially in women under 50 and especially in cancers under 1 cm in size.

Controversy over Mammography

There has been no evidence to date that the Health Insurance Plan study, using clinical examination and mammography with the techniques considered optimum at the time, has reduced mortality from breast cancer in women under 50. Whether the NCI-ACS screening programs with improved mammographic techniques will show any such reduction is hypothetical. Since there are no control groups in these studies, no data on mortality can be derived.

Critics of mammography maintain that since apparently well women under the age of 50 are subjected to a potential radiation hazard by mammography, with no potential benefit in mortality reduction, the hazard presumably exceeds the benefit. That is the essence of the mammography controversy.

There is general agreement in two areas:

1. In the symptomatic woman with a dominant mass, localized pain, or nipple discharge, the real possibility of cancer exists. All diagnostic means, including mammography, must be used for elucidation of the problem.

2. Since the Health Insurance Plan study demonstrated a substantial reduction in mortality in women over 50 (40 per cent in this group), the great value of mammography as part of a periodic screening program in this age group has been widely recognized. Particularly with the newer low dosage mammography techniques, it has been widely accepted that mammography is proper and necessary as part of a routine health examination in all women over 50.

Real disagreement exists as to whether mammography is ethically indicated in women under 50 who are truly asymptomatic. It is generally agreed that such women who have the substantial risk factors of previous breast cancer or positive family history in mother or sister should have a periodic complete examination, including mammography. Of course, since breast cancer is uncommon in women under 35, they should be excluded unless medical suspicion of breast disease warrants mammography.

The problem in the younger asymptomatic woman revolves around two facts:

1. The breast is sensitive to X-radiation. Previous studies of women subjected to substantial doses of radiation, such as with the atomic bomb, fluoroscopies in the course of treatment for tuberculosis, or radiation treatment for breast abscess, have indicated increased incidence of the disease in those exposed. Initiation of such breast cancer had a latent period of about 10 years and varied in proportion to dose. Although no evidence exists for absence of a threshhold dose, it has been considered prudent that such a dose be postulated and that a linear radiation effect be assumed down to the smallest quantity of radiation. A fair statement of radiation risk from mammography has been offered by Dr. Arthur Upton, noted radiobiologist and present Director of the National Cancer Institute: "One rad to the body of the breast given to a million women would produce 6 cancers per year for a lifetime of the woman after a latent period of 6–10 years."

2. There has been no evidence to date that the Health Insurance Plan study, using clinical examination and mammography with the techniques considered optimum at the time, has produced any reduction in mortality from breast cancer in women under 50. Whether such a state of affairs would exist in the NCI-ACS screening programs with the improved mammographic techniques being used must be considered to be pure supposition.

In considering risk versus benefit in mammography, emphasis should be placed on two additional factors.

RISK OF RADIATION. Risk is directly proportional to dose. The state of the art in mammography has changed radically in the years since the Health Insurance Plan study. In that study doses of 8 rads to the skin were given per examination. New film-screen techniques, as used at Guttman Institute and other places, now deliver 0.2 to 0.3 R to

the skin per exposure or, as we have noted above, doses of about .02 to .03 rads to the mid breast for two views. Using .02 to .03 rads for a complete examination of the breast, instead of 1 rad in the formula mentioned above, means that if all 40 million women at risk for breast cancer in this country were to receive a breast examination, including mammography, every year for the 30 years that the youngest member would be exposed, the following would happen. The present incidence of 90,000 breast cancers would be found, resulting in 34,000 deaths per year. With screening (using mammography plus palpation) we would reduce the death rate by at least one-third or save 12,000 lives. The loss of life from the radiation would involve 6 patients per year or 180 patients in the 30 years of lifetime, after a 10 year latent period, and one-third of these too would probably be saved. In other words, *at least* 12,000 women would be saved at a cost of, *at most*, 120 lives over 30 years. Such dosage is negligible by all radiologic standards and should permit more liberal interpretation of risk versus benefit.

Benefit of Mammography. The absence of statistical mortality benefit in the under 50 age group is an important factor in the guidelines limiting mammography in this age group. In the Health Insurance Plan study more cancers were found in the study group than in the control group in women under 50 by age at diagnosis, yet the numbers of cancers at the age of death were the same. Perhaps in women under 50, cancers of the more localized type, found particularly on mammography in the study group, might have been detected over the age of 50 at a more advanced stage if no screening program were available. Perhaps screening women under 50 in that study helped to keep the death rate down in those over 50. This concept is being investigated further. It may elucidate the perplexing question of why mortality benefit was demonstrated only in women over 50 years of age.

Symptomatic Women. The guidelines specifically exclude women with any symptoms "whatsoever." This gray area needs further clarification. When does a lump, pain, or nipple discharge make a woman symptomatic? Is a single lump a symptom and lumpiness or multiple lumps not? Is a localized persistent pain a symptom and diffuse intermittent pain not? Is a free-flowing dark discharge a symptom and a discharge produced by nipple pressure not? Is the symptomatic woman the one who goes to a physician for a breast examination and not the one who goes to a breast center such as the Guttman Institute? These are important considerations, certainly in the mind of the woman. Minor symptoms are commonplace. When we consider that most cancers are found under screening auspices in women under 50 as well as over 50 with only minimal symptoms or none at all, can we not begin to be more liberal with our interpretation in light of the low breast radiation dose?

CONCLUSION

Disagreement may exist among experts as to what is a "killing cancer," what represents a "true" cancer, how such cancers should be

treated or whether they should be treated, or what the best treatment is for an invasive killing cancer of different pathologic types in women of different ages or emotional or psychic backgrounds. However, there is general agreement that the earlier a breast cancer is detected and treated, the more women will survive the disease or be cured. There is also general agreement that early detection involves at least three general principles:

Since advancing age is the most important risk factor, since most breast cancer is detectable in women over the age of 50, and since definite proof in this age group exists that screening for the disease will lower the death rate by at least 40 per cent, and that mammography as well as palpation are necessary for such reduction, it is imperative that screening using both modalities become a routine part of the medical examination of all women over 50 on an annual basis.

Since the symptomatic woman with a dominant mass, persistent pain, or nipple discharge may have these symptoms because of an underlying cancer, all such women should have a complete breast examination to include mammography or any other diagnostic study as often as is necessary to determine whether cancer is present.

Mammographic technique used under all circumstances should be the one producing the greatest detail and resolution, with the lowest amount of radiation needed to produce high quality films. Such techniques should be subject to change as new knowledge and technology provides improvement in these areas.

Techniques are already readily available and in use which deliver doses as low as .02 rads to the mid breast. This low dosage can be considered to be negligible in comparison with the presumed benefit from mammography.

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Preoperative Assessment of the Patient with Breast Cancer

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The preoperative assessment of the patient with a breast mass begins with a history and physical examination. A freely mobile, nontender mass in a 20 year old female is probably a fibroadenoma and requires nothing more than excision under local anesthesia. Similarly, an intermittently tender mass in the breast of a 30 year old female is frequently cured by simple needle aspiration of fluid and, again, no further diagnostic or therapeutic procedures are necessary. Any mass that is suspicious of malignancy, however, should be clinically staged. Accurate clinical staging will identify at least some of the patients with apparent local disease who have metastases. Needless radical surgery will thus be avoided. Clinical staging also provides a reasonably accurate estimate of the patient's prognosis. In addition, it provides the clinical investigator with a means of comparing one type of treatment modality to another.

Since clinical staging is based on physical findings, the TNM Classification System developed by the American Joint Committee for Cancer Staging and End Results Reporting is briefly reviewed.[10] On the basis of clinical stage, the chances of systemic metastases are estimated. This information is then correlated with the chances of detecting metastases by currently available screening techniques.

CLINICAL STAGING

A breast mass that is 2 cm or less in its maximum dimensions and is not associated with clinical evidence of axillary lymph node metastases is classified as a Stage I lesion ($T_1N_1M_0$). Patients with Stage I breast cancer have an 80 per cent chance of 10 year survival. A breast lesion less than 2 cm in size but associated with clinical evidence of

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axillary lymph node metastases, or a mass that is 2 to 5 cm in size either with or without clinical evidence of axillary lymph node metastases, is classified as Stage II ($T_1N_1M_0$, $T_2N_0M_0$, or $T_2N_1M_0$). These lesions are associated with a 60 per cent chance of 10 year survival. Primary tumors that are greater than 5 cm in their greatest dimensions or primary tumors that have extended to the skin of the breast or the chest wall are classified as Stage III lesions. Extension to the skin is manifested by skin retraction, dimpling, ulceration, or the presence of satellite skin nodules. Extension to the chest wall is characterized by fixation to the chest wall. The chance of 10 year survival is slightly less than 30 per cent in patients with Stage III breast cancer.

Further considerations in management after the initial clinical staging are dependent upon an estimate of the chances of metastases being present and also an estimate of the size of the metastatic lesions and therefore the chance of detecting them. As indicated by the correlation of survival figure with clinical stage, the incidence of occult metastases varies considerably with the clinical stage of disease. Only 20 per cent of patients with Stage I breast cancer have occult metastases, whereas greater than 70 per cent of patients with Stage III disease have occult metastases. Patients with Stage II disease fall in an intermediate category; these patients have an approximate 40 per cent incidence of occult metastases. Since metastatic lesions less than 2 to 3 cm in size are difficult to detect by currently available screening methods, the size of a potential metastatic lesion must also be considered in planning subsequent management.

Folkman[19] has demonstrated experimentally that tumors can live by diffusion alone until they are composed of approximately 100,000 cells. Survival beyond this stage required vascularization and once vascularization has occurred, metastases are theoretically possible. Therefore the primary tumor must have a population of at least 100,000 cell before metastases start growing. DeWys[12] and Simpson-Herren[35] have demonstrated experimentally that primary and metastatic tumors grow at approximately the same rate. Similar clinical results in patients with breast cancer have been reported by Charbit.[8] These experimental and clinical studies indicate that a continued difference in the size of the primary tumor versus its metastases will be maintained. Thus a metastatic lesion that measured 1 cm in diameter and would be composed of 5×10^8 cells, would have to be derived from a primary tumor which, if growing at the same rate, would be 5 cm in diameter and composed of 1.5×10^{11} cells. This type of experimental data gives some insight into the problems associated with the detection of clinically occult metastases. Metastatic lesions from tumors less than 5 cm in size are rarely greater than 1 cm in size and therefore are difficult to detect.

COMMON SITES OF METASTATIC DISEASE

Once the chances of occult systemic metastases and the size of these potential metastases have been estimated, the common sites of

metastatic disease must be considered. Although breast cancers can metastasize to almost any site in the body, the commonest sites of metastatic disease are the bones, lungs, mediastinal lymph nodes, and liver. Metastatic lesions in these organs begin as a cluster of cells which, as previously noted, probably grow at about the same rate as the primary tumor.

Lung metastases can occur in two general patterns; the specific pattern relates to the initial mode of spread. Predominantly blood-borne metastases will lodge in a pulmonary capillary, grow through the wall of the capillary, and gradually grow into a nodular mass. This is the most common form of pulmonary metastases and the lesion will eventually produce a single or, more commonly, multiple nodular densities seen on the chest radiograph. These densities are not visible on routine screening films until they become 1 to 2 cm in size. Metastatic breast cancer in the mediastinal lymph nodes can spread in a retrograde fasion into the peribronchial lymphatics, thus producing a lymphangitic pattern of spread seen on the chest radiograph. In these cases, chest radiographs are characterized by a diffuse interstitial infiltrate that is difficult to diagnose until the tumor has spread rather diffusely throughout the lung. Nodular lesions usually produce no symptoms until the lung is largely replaced with metastatic tumor. Lymphangitic spread can produce an irritating cough and increasing shortness of breath in the later stages of the disease.

Metastatic lesions in the mediastinal lymph nodes will not be visualized by chest radiographs until they reach 2 cm in size. This occurs because the lesions tend to blend in with the other mediastinal structures. These lesions remain asymptomatic until the tumor grows out of the node and invades adjacent structures such as the recurrent laryngeal nerve or the esophagus.

Osseous metastases are the commonest sites of metastatic breast cancer in autopsy series and at least 20 per cent of patients with operable breast cancer will eventually develop clinical evidence of osseous metastases prior to death.[4] Osseous metastases occur from blood-borne metastases either systemically through the lungs and left heart or via the intercostal veins and disseminate by way of the vertebral veins. The pelvis and spine are the most frequent sites of metastatic disease. Within the spine the lumbar spine is the commonest site of metastases followed by the thoracic spine, sacrum, and cervical spine. Other common sites of metastases in order of decreasing frequency are the femur, ribs, skull, humerus, scapula, and clavicle.

Haagensen[23] has identified four types of bone metastases. The commonest type of osseous metastases is the osteolytic lesion which destroys bone mineral. This lesion produces an irregular lytic lesion on the radiograph, but at least 50 per cent of the bone mineral must be destroyed before the lesions are apparent on the radiograph. The increased osteoclastic activity initiated by the bone destruction will also produce an increased accumulation of radioactivity on bone scan. In contrast, osteoblastic lesions produce a thickening of the trabecular pattern which eventually coalesce to form radiographic evidence of irregular dense masses. Only 5 to 10 per cent of metastases from a

breast cancer are osteoblastic. The third type of metastatic lesion produces no radiographic or scan evidence of metastases. These intertrabecular types of metastases are produced by malignant cells growing into the bone marrow without any associated damage to the adjacent bone. The fourth type of metastases is any combination of the other three types. Bone metastases remain asymptomatic until the metastatic lesions extend to the periosteum. Periosteal distention or periosteal invasion produces pain and less frequently tenderness in the involved area.

Liver metastases are present in 60 to 70 per cent of patients dying of metastatic breast caner.[24] Metastatic lesions occur when clusters of cells lodge in a capillary fed by the hepatic artery. These early metastatic lesions gradually grow into nodular lesions.Symptoms are rarely produced in the early stages of metastatic disease. Symptoms, when they occur, are either due to distention of Glissen's capsule or obstruction of the biliary system producing jaundice. Small liver metastases are rarely detected by physical examination; even at autopsy the liver is of normal size in 30 per cent of patients with hepatic metastases.[31]

ROUTINE SCREENING PROCEDURES

The number of routine screening procedures varies according to the clinical stage of disease. Primary tumors less than 5 cm in size without clinical evidence of axillary lymph node metastases are rarely associated with metastases that are greater than 1 cm in diameter and therefore detectable by currently available screening methods. Conversely, primary tumors greater than 5 cm in size or tumors with demonstrable local invasive properties have a much greater chance of metastases, and the chances of the metastatic lesions being greater than 2 cm in size are also considerably increased.

In any patient with suspected or proven breast cancer, several routine studies are indicated as general screening procedures regardless of the stage of disease. A chest x-ray film is a relatively inexpensive procedure that results in little irradiation of the patient. Although it is unusual to detect occult pulmonary mediastinal pleural or osseous metastases, the chest films should be carefully scrutinized for radiographic evidence of nodular parenchymal lesions, interstitial infiltrates, mediastinal widening, pleural effusion, or osteolytic or osteoblastic lesions in the bones visualized by the x-ray film. Additional studies such as oblique films and tomograms are not indicated unless a suspicious lesion is detected by a relatively high kilovoltage film (130 to 150 kVp).

In my opinion, only one other screening procedure is indicated in all patients with suspected or proven breast cancer — a serum alkaline phosphatase. This isoenzyme originates in the liver, bone, intestine, kidney, and placenta of pregnant women. Elevations of the serum alkaline phosphatase are most often due to increased amounts of liver and bone enzyme. Numerous investigators[7, 26, 38] have demonstrated that the serum alkaline phosphatase is elevated in 58 to 90 per cent of patients with liver metastases, thus indicating that the serum alkaline

phosphatase is a relatively sensitive indicator of liver metastases. It is not a specific indicator of metastatic lesions, however. A number of other hepatobiliary disorders can raise the serum alkaline phosphatase as well as inflammatory lesions in bone, metastatic lesions in bone, normal growth of bone, and osteoporotic bones. Nevertheless, the serum alkaline phosphatase has proved to be a very useful screening procedure for either bone or liver metastases if it is interpreted in conjunction with other liver enzymes.[30] Clinical series reported by Fenster,[16] Ferrante,[17] and Smith[37] indicate that the serum alkaline phosphatase is as accurate as a liver scan in detecting liver metastases from a variety of primary tumors. Significant elevations of the serum alkaline phosphatase in the presence of a normal bilirubin and serum glutamic oxaloacetic transaminase are suspicious enough of bone or liver metastases to indicate the need for additional studies of the skeleton and liver.

LIVER SCANS

Liver scans are obtained following the injection of a sulphur colloid labeled ^{99m}technetium. The colloid particles are taken up by the reticuloendothelial system, and since the Kupffer cells of the liver represent at least 90 per cent of reticuloendothelial activity in the body, the radioactivity in the colloid particles provides a means of screening the liver. Metastatic lesions in the liver parenchyma are most accurately diagnosed by detecting focal filling defects. Diffuse infiltrative lesions that do not destroy or displace a significant number of functioning Kupffer cells cannot be detected.

Ackerman[1] has demonstrated experimentally that single parenchymal defects smaller than 2 to 2.5 cm in diameter could not be routinely detected by liver scanning. A surprising number of patients with metastatic breast cancer have hepatic lesions less than 2 cm in size, and even at autopsy, Ozardo[31] reports that 30 per cent of patients dying of metastatic breast cancer have lesions less than 2 cm in size. The majority of clinical studies evaluating liver scans have employed a patient population with either known recurrent cancer or a high probability of metastatic disease, not patients with small, asymptomatic lesions. Lunia[28] describes 44 patients with breast cancer in whom the scans were positive for metastases in 17 and negative in 27. The diagnosis of liver metastases was correct in 70 per cent of the patients studied and incorrect in 23 per cent. These results were confirmed within a mean period of 40 days by autopsy in 19 patients, hardly a group of patients with operable breast cancer. Drum[13] reports a similar group of 125 patients with breast cancer, 67 per cent of which were found to have metastases confirmed by needle biopsy, exploratory laparotomy, or autopsy. Although these studies as well as those reported by a number of other investigators[11, 14, 18, 22] have demonstrated that liver scans can detect 80 per cent of metastatic lesions in patients with advanced cancer, they do not indicate the efficiency of liver scans in detecting metastases in patients with small operable cancers.

Sears[34] has described a clinical study that evaluated 100 patients with operable breast cancer. Only one of these patients proved to have liver metastases that could be detected by a preoperative liver scan. On the basis of these results, liver scans do not appear to be indicated as routine screening procedures in patients with otherwise operable breast cancer who have a normal serum alkaline phosphatase. Liver scans are indicated, however, if the serum alkaline phosphatase is significantly elevated.

Recent studies by McCartney[29] and Sugarbaker[39] have demonstrated the accuracy of combining the liver scan and serum carcinoembryonic antigen (CEA). McCartney's studies looked at a variety of liver lesions including benign as well as malignant lesions.[29] These studies demonstrated that all patients with a positive liver scan and a CEA greater than 9 ng per ml had liver metastases, whereas only 4 of 291 patients with negative scans and CEA levels less than 9 ng per ml were later found to have liver metastases. Similar results have been reported by Sugarbaker[39] in a study of 55 patients with breast cancer, most of whom apparently had known recurrence or metastases. In Sugarbaker's study, liver scans were correlated with CEA levels greater than 2.5 ng per ml. If these two tests were abnormal, there were no false positive results, i.e., all of the patients had liver metastases. This combination of liver scans and relatively low levels of CEA did not decrease false negative results; three patients with liver metastases had normal liver scan and only a minimally elevated CEA. On the basis of these recent reports, the CEA appears to be most useful in further defining the etiology of focal defects detected by the liver scan. If the focal scan defects are associated with CEA levels greater than 5 ng per ml, liver metastases are considered to be present. Focal defects on the liver scan that are not associated with significant elevation of the CEA should be further evaluated by percutaneous needle biopsy, peritoneoscopy, or a laparotomy.

BONE SCANS

As previously noted, the skeletal system is the commonest site of metastatic disease in patients dying of breast cancer. A significant number of these osseous metastases are difficult to detect, however, prior to death. At least 50 per cent of lesions found at autopsy are not seen on x-ray films taken shortly before the patient's death. Similarly, bone metastases are difficult to detect radiographically in the living patient, particularly if the bone lesions are small and are not causing symptoms. Gibbons[21] was unable to detect any radiographic evidence of skeletal metastases in 85 consecutive patients with operable breast cancer. Similarly, Roberts,[33] in a retrospective study of 114 patients with T_1 and T_2 lesions, found only two patients with radiographic evidence of metastases. The failure of radiographs to detect metastatic osseous lesions, particularly when they are quite small, is related to a number of factors. Some of the metastatic lesions are intertrabecular and therefore not visible on x-ray film. Of greater significance is the

fact that at least 50 per cent of bone mineral must be destroyed before metastatic lesions can be detected by a radiograph, and in lesions of the spine, even a greater percentage of bone mineral must be destroyed.[2]

In spite of the fact that radiographic skeletal surveys are normal in almost all patients with operable breast cancer, at least 20 to 30 per cent of these patients will develop clinical and radiographic evidence of metastases within the 10 years following treatment.[4, 32] Since radionuclide bone scans are known to detect metastatic lesions many months prior to the time they are detected by conventional radiography, bone scans initially at least seem to offer a more promising means of detecting these otherwise occult osseous metastases.

Bone scans are obtained by the following technique. Whole body images are obtained with a rectilinear scanner after the intravenous injection of ^{99m}Tc phosphonate and diphosphonate. These rectilinear scans are supplemented by gamma-camera images of the entire spine plus any area that is asymptomatic or equivocally abnormal on the rectilinear scan. If the bone scans are interpreted as normal, no additional studies are performed. It is extremely important to obtain radiographs of any area of increased radioactivity detected by the bone scan. If radiographic evidence of a bone lesion such as degenerative joint disease or Paget's disease is found to be the cause of the increased activity, the bone scan is considered to be negative for metastatic disease. Only those bone scans that are associated with normal radiographs or radiographic evidence of metastases are considered to be positive for metastases.

Our experience at Johns Hopkins with 64 patients with Stages I and II breast cancer ($T_1N_0M_0$, $T_1N_1M_0$, and $T_2N_1M_0$) demonstrated that preoperative bone scans detected occult osseous metastases in only 1.8 per cent of the patients studied.[3] A similarly low incidence (2 to 4 per cent) of positive bone scans in patients with T_1 and T_2 lesions has been reported by El-Domieri,[15] Green,[23] Gerber,[20] Lentel,[27] and Butzelarr.[5]

In contrast, investigators from this country, Hoffman[25] and Sklaroff,[36] and three investigators from Britain[6, 9, 33] have reported a remarkably higher incidence of positive bone scans in patients with otherwise operable breast cancer (Table 1). Hoffman and Sklaroff's higher incidence of positive bone scans is probably explained by a difference in stages of disease. Hoffman's results of 40 per cent positive bone scans in patients with operable disease are readily explained by the high incidence of axillary lymph node metastases in his series (78 per cent) and by the fact that the patients were screened as long as three months following mastectomy and axillary lymph node dissection. Sklaroff's incidence of 14 per cent positive bone scans in 64 patients is also probably explained by the fact that his series consisted solely of patients with histologic evidence of axillary lymph node metastases. The results from Britain are more difficult to explain and may be related to differences in interpretation of the bone scan. The clinical stage of disease and length of follow-up are comparable to the stages of disease and length of follow-up in our group of patients and also those reported by El-Domieri,[14] Green,[22] Gerber,[19] and Butzelaar.[5]

Table 1. *Incidence of Positive Bone Scans in Patients with Stages I and II Breast Cancer*

AUTHOR	STAGE	NO. OF PATIENTS	PER CENT POSITIVE
Baker[3]	I and II*	64	1.8
Gerber[19]	I and II*	110	2
Green[22]	I and II*	71	4
El-Domieri[14]	I and II*	24	4
Butzelaar[5]	I and II*	90	3.4
Hoffman[24]	I and II†	47	40
Sklaroff[35]	II†	64	14
Citrin[9]	I and II*	75	14
Roberts[32]	I and II*	46	22.9
Campbell[6]	I and II*	80	35.5

*Clinical stage.
†Pathologic stage.

Citrin's,[9] Roberts',[32] and Campbell's[6] greater incidence of positive bone scans may be related to a peculiarly high incidence of osteolytic lesions in their series compared to a higher incidence of intratrabecular and osteoblastic lesions in our series and those that agree with it. I have no other explanation for the discrepancy in results. Campbell[6] describes very convincing evidence that the bone scan, in his hands, at least, has detected clinically occult disease. Fifty-four per cent of scan-positive and scan-suspicious patients have developed evidence of disseminated disease within 12 months of the scan.

On the basis of our results and the majority of investigators outside of Britain, I have concluded that bone scans are not indicated as routine screening procedures in patients with T_1 and T_2 lesions. It does not seem reasonable to perform a screening procedure that has less than a 5 per cent chance of detecting a clinically occult lesion. Other investigators such as Gerber and associates,[20] however, disagree with this opinion and advocate routine bone scans in patients with T_1 and T_2 lesions, even though they report only a 2 per cent incidence of positive scans. Gerber[20] argues that preoperative scans are valuable because they can be compared with subsequent scans taken during the follow-up period. Current clinical experience, however, indicates that only 20 per cent of patients with T_1 and T_2 lesions will develop bone metastases and therefore only 20 per cent of patients might benefit from such baseline studies. Furthermore, to my knowledge, there is no evidence that the detection and treatment of small asymptomatic bone metastases will necessarily increase either the length or quality of survival of patients with breast cancer.

I do advocate routine bone scans as screening procedures for occult osseous metastases in patients with Stage III lesions (T_3 or T_4, N_0 or N_1, M_0). Our experience with this type of patient indicates an appreciable incidence of positive scans — 24 per cent in 41 patients with

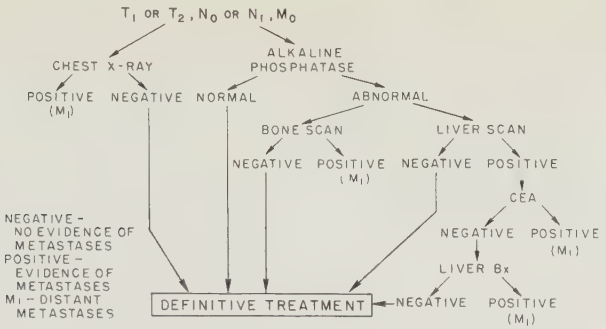

Figure 1. Clinical assessment of patients with stages I and II breast cancer.

Stage III disease. Similar results have been reported by El-Domieri[15] and Gerber.[20]

SUMMARY

The clinical assessment of patients with Stages I and II breast cancer is outlined in Figure 1. A chest x-ray film and serum alkaline phosphatase are the only routine studies indicated. If the serum alkaline phosphatase is abnormal in the presence of otherwise normal liver function studies, a bone scan, liver scan, and CEA should be obtained. Areas of increased radioactivity on bone scan are always evaluated by additional radiographs and in some cases tomograms. The majority of focal areas of increased radioactivity will demonstrate radiographic evidence of benign bone lesions, predominantly degenerative joint disease. Only those focal areas of increased radioactivity that are normal on x-ray film or show radiographic evidence of metastases are considered to be positive for metastatic disease. The results of the

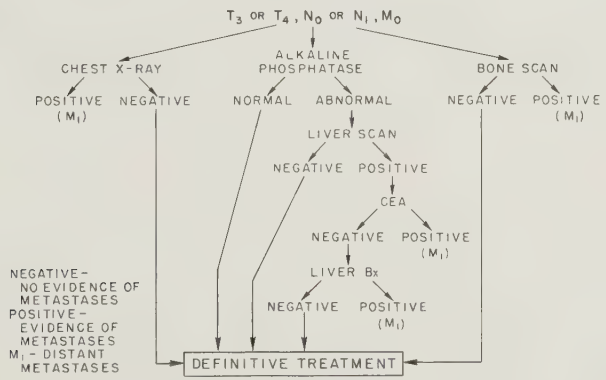

Figure 2. Clinical assessment of patients with stage III breast cancer.

liver scan are correlated with the level of CEA. Focal areas of decreased radioactivity associated with a CEA greater than 5 ng per ml are considered to be metastases. In the absence of elevation of the CEA, focal areas of increased radioactivity should be biopsied prior to any further considerations as to definitive therapy.

The clinical assessment of patients with Stage III disease is outlined in Figure 2. Patients with this stage of disease have a much greater chance of having clinically occult metastases of sufficient size to be detected by chest x-ray film, serum alkaline phosphatase, and bone scan. If the serum alkaline phosphatase is abnormal, a liver scan and CEA are obtained in an effort to detect liver metastases. The same sequence of events is then followed as suggested for patients with Stages I and II disease.

Several new techniques of detecting occult metastases are being evaluated. Biomarkers are the subject of another article in this volume. The use of computerized axial tomography is also being evaluated as a means of detecting lung, liver, and mediastinal metastases. The results of these initial clinical trials should be carefully followed.

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Immunology, Tumor Markers, and Breast Cancer

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The past decade has seen some exciting developments in the field of tumor immunology. Immune responses, cellular and (or) humoral, have been demonstrated for a wide variety of human tumors including breast cancer. It remains to be proved, however, whether these tumor immune responses in man have any diagnostic, prognostic, or therapeutic implications and whether they relate to the natural history of a given tumor.

The concept of an immunologic aspect to human breast cancer, although lacking direct evidence, is supported by a number of observations made over the past several years. Indeed, Black[2] has cited breast cancer as a "model for cancer immunology" based on histologic characteristics of tumors and axillary lymph nodes, and on skin reactivity of patients to microtome sections of their own tumors. The variable nature of the disease itself has led to speculation of immunologic involvement. In some cases, patients may demonstrate long disease-free intervals followed by periods of rapid tumor growth, consistent with an immunologic process restraining tumor proliferation until some unidentified factor disrupts host-tumor homeostasis. Our attempts to elucidate these prognostic factors, immunologic or otherwise, have not been successful so far. The purpose of this presentation is to review clinically relevant studies of human breast cancer dealing with immunopathology, tumor-related markers, immunologic responses of patients, and immunotherapy.

IMMUNOPATHOLOGY

Suggestion of an immunologic parameter to breast cancer has its

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foundation in histopathologic examination of both tumor and regional axillary lymph nodes. In 1945, Moore and Foote[30] discussed the relatively favorable prognosis of medullary carcinoma of the breast and added that the significance of lymphocytic infiltrates in tumor had been recognized at least 20 years previously. Favorable prognosis has also been associated with a regional lymph node pattern of sinus histiocytosis as described by Black et al.[3] More recently, studies of regional lymph node histology in breast cancer, other than sinus histiocytosis, have not concurred with respect to clinical significance of patterns. Tsakraklides et al.[51] examined 277 cases and cited a pattern of lymphocyte predominance in regional lymph nodes as being common to cases with good survival, whereas lymphocyte depletion was more frequently associated with poor prognosis. However, Fisher et al.,[12] after studying 303 cases, found no prognostic value in assessments of regional lymph node histology. The issue remains to be resolved.

TUMOR MARKERS AND CANCER DETECTION

Biochemical Markers

In the search for tumor markers in breast cancer a variety of approaches have been pursued, including analyses of metabolic byproducts, oncofetal antigens, virus particles or related macromolecules, plasma proteins, hormones, and cell-associated components of breast carcinoma tissue. In a recent review, Tormey and Waalkes[50] outlined several biochemical markers which, although not diagnostic, were found to be elevated in patients with metastatic breast disease. Among these markers were polyamines, putrescene and cadaverine, and transfer RNA nucleosides such as pseudouridine. Markers most frequently encountered in disseminated disease, however, were human chorionic gonadotropin and carcinoembryonic antigen, which were elevated in 47.8 and 65.2 per cent of patients respectively.

Carcinoembryonic Antigen

Carcinoembyronic antigen (CEA) is a glycoprotein that has been detected in a variety of malignant and nonmalignant disease states. In spite of its relative nonspecificity, it has proved to be a helpful marker in following known cancer patients postoperatively. With respect to breast cancer, CEA is not detectable in all cases, but when present can be a valuable tool for clinical monitoring of the patient. Steward et al.[47] found CEA titers to parallel patient response to treatment, with increased values in poor responders and low titers maintained in patients with good therapeutic response. Elevated CEA levels following mastectomy have been associated with a high frequency of disease recurrence and with the presence of disseminated disease, especially hepatic metastases.[54] In a large study of 824 postoperative patients, Myers et al.[32] found 60.2 per cent of patients with Stage IV cancer to have elevated CEA and CEA levels correlated with disease recurrence.

Viral Markers

The rationale for consideration of viral markers in human breast cancer stems from recognition of the viral etiology of murine mammary carcinoma. Speigelman and others[45] have summarized studies utilizing sophisticated biochemical analyses in which RNA from human breast cancer tissue was found to have homology with DNA synthesized from the RNA template of murine mammary tumor virus (MMTV). No homology was found with other murine oncogenic viruses, and RNA from other types of human tumors did not show homology with MMTV-produced DNA. Such data have been interpreted as indicative of viral genomic information present in mammalian breast tumor cells. Other findings by Speigelman et al.[45] suggest involvement of an RNA virus in breast cancer by detection of a virally-induced enzyme, reverse transcriptase, which catalyzes the formation of DNA from viral genomic RNA. Speigelman found this enzyme to be present in 79 per cent of 38 adenocarcinomas, but in none of 10 benign breast tissue specimens.

The clincial potential of a major MMTV glycoprotein (gp47) as a diagnostic or prognostic marker was investigated by Zangerle et al.[58] using a sensitive radiolabeled technique. Sera of 314 individuals, including 107 normal individuals and 89 breast cancer patients, were analyzed for presence of gp47 and none was positive. Although the study clearly demonstrated the presence of gp47 in sera of MMTV-infected mice, this viral protein does not appear to have relevance to the human disease.

Serum Proteins

Serum ferritin concentrations may be increased in many types of tumors and also in nonmalignant gastrointestinal or hepatic disorders. High ferritin levels have been associated with recurrent breast cancer, suggesting that measurement of serum ferritin may have prognostic value.[28] Detection of circulating immune complexes in serum of breast cancer patients has been described by Rossen and associates[43] who, unfortunately, found no correlation between the presence of complexes and clinical status of 27 patients. Contrasting results have been reported by Hoffken et al.[18] in a retrospective study of small group of breast cancer patients tested preoperatively and at 12 months post mastectomy. Patients with involved lymph nodes and those who had expired within 23 months after surgery had elevated titers of complexes when compared with values of patients with tumor-free nodes. However, when the poor prognosis groups were compared with age-matched controls, significant differences were not apparent, making this study difficult to interpret.

Cell-Associated Markers

Identification of cell-associated, breast tumor markers in many cases has relied on evidence that such markers provoked an immunologic response either in vivo or, more indirectly, in vitro. Skin testing with autologous breast cancer and benign tissue extracts was per-

formed by Hollinshead et al.[19] After fractionation by column chromatography and gel electrophoresis, a cellular component was obtained to which 10 out of 12 breast tumor patients reacted, whereas none of 8 patients with other cancers reacted, suggesting that a specific breast tumor antigen had been isolated. Using an in vitro leukocyte adherence inhibition assay as an indicator of immune reactivity, Lopez and Thompson[27] have recently isolated an "antigenic" factor of 80,000 to 150,000 molecular weight from serum of tumor patients. Another "antigenic" factor of 48,000 molecular weight was purified from urine, suggesting that enzymatic degradation of the serum component had occurred prior to glomerular filtration.

Chemical analyses of eluates from gel-separated sections of mammary carcinomas by Zachrau et al.[57] produced evidence of a 50,000 molecular weight component which was present in tissue from 65 per cent of 64 patients, and 2 of 7 eluates from benign breast tissue. This compound was further delineated as having three different forms, depending upon migration in an electrophoretic field. A slow fraction was most frequently associated with Stage I tumors of nuclear grade 3, or with the presence of perivascular infiltrates and sinus histiocytosis. The fast component was more often seen in cases of poor prognosis. Edgington and associates[10] isolated a cytoplasmic glycoprotein of 25,000 molecular weight from metastatic breast carcinomas but the clinical relevance of this glycoprotein has not yet been established.

As a final comment, hormone receptors should be considered in the category of breast tumor markers and cell-associated components. In a study of 145 patients, Knight and others[25] noted that the single most important prognostic factor of early disease recurrence in breast cancer was the presence or absence of estrogen receptors. Early recurrence (18 months post mastectomy) occurred in 34 per cent of 54 estrogen receptor-negative cases and in only 13 per cent of 91 receptor-positive patients.

IMMUNOLOGIC ASSAYS AND PROGNOSIS

General Immunologic Competence

Commonly used assays that provide data regarding overall immunologic competence include delayed hypersensitivity skin tests with common recall antigens, lymphocyte counts, concentrations of T and B cells, in vitro lymphoctye transformation assays with mitogens and common recall antigens, and serum immunoglobulin levels. Failure to demonstrate normal patterns by the above methods may indicate compromise of immunologic potential. Most investigators have agreed that one or more of the above parameters are abnormally depressed in the tumor-bearing state and that abnormality increases with disease progression.

Significant impairment of skin test reactivity to a battery of common antigens was observed in metastatic breast disease by Nemoto et al.,[34] and Stein et al.[46] also noted a trend toward fewer positive skin

tests in advanced disease. Use of skin testing as a prognostic indicator, however, has generally met with unfavorable results inasmuch as many patients with recurrent disease may show normal reactivity.[34, 46, 53]

Lymphocyte transformation assays commonly use nonspecific mitogens such as phytohemagglutinin (PHA) and concanavalin A (Con A) which primarily stimulate T cells, and pokeweed (PWM) which stimulates both B and T cells. Common recall antigens used in skin testing may also be used for lymphocyte transformation and specifically stimulate memory cell mitosis in vitro. Such reactivity correlates with in vivo skin test response and has been noted to be severely or partially impaired in advanced breast cancer.[34] Lymphocyte reactivity to mitogens has also frequently been found to be depressed in advanced disease, and Wanebo et al.[53] noted a linear trend of decreasing PHA responsiveness in conjunction with increasing tumor burden. PHA-induced blast transformation has been reported to be depressed even in early stages of disease, suggesting that the tumor-bearing condition exerts a general, nonspecific depression of immune function.[56] Whittaker and Clark[56] attributed this general immunodepression to the presence of inhibitory serum factors. Whitehead and Hughes,[55] on the other hand, found no relationship between PHA response and clinical status, noting that many patients with normal responses and recurrent disease and many others, who were disease-free at three years post mastectomy, had poor reactivity.

Quantitation of T and B lymphocytes in breast cancer has produced somewhat disappointing results. A number of studies have failed to detect any direct correlation between percentage of T cells and clinical status.[34, 53] Keller et al.,[24] however, did report significantly lower T cell numbers in breast cancer patients in general than in individuals with benign disease. Absolute lymphocyte counts may be of prognostic value according to Papatestas and associates,[36] who found five-year survival to be associated with pretreatment lymphocyte counts of greater than 2000 per mm^3. In this retrospective study of 453 patients, higher pretreatment counts were also found in earlier stages of disease. Moroz et al.[31] recently noted a subpopulation of ferritin-bearing leucocytes appearing in Stages I and II breast cancer but not in Stage III or benign disease. The clinical value of these promising observations remains to be clarified.

Circulating immunoglobulins have also been measured in breast cancer. Meyer et al.,[29] in an uncontrolled study, noted increased IgA in radiation treated, disease-free patients, whereas disease recurrence correlated with decreased IgA levels. IgA was also found to be elevated by Roberts et al.[41] in 92 breast cancer patients of various stages who were compared with 50 age-matched, normal, and benign disease controls. In addition, IgG levels were significantly decreased in the malignant disease group.

A critical problem in evaluating any immunologic data in cancer patients is posed by the potentially deleterious effects of radiation or chemotherapy on the immune system. Stjernswärd et al.[49] examined

patients with mammary carcinoma before and after irradiation and noted lymphopenia, depressed PHA responses, and shifts in T and B cell concentrations lasting for at least one year after treatment.

Immunologic Competence of Regional Axillary Lymph Nodes

Based upon histologic observation, regional axillary lymph nodes in breast cancer have long been thought to participate in some immunologic tumor-related activity, and a number of in vitro techniques have been applied to regional node cells in attempts to define cell populations, immunologic competence, and other immunologic parameters of possible prognostic value. Reactions of these lymphocytes with autologous tumor cells have been examined at our institution using a qualitative in vitro method.[9] Significant lymphocyte-tumor cell interaction, defined as clustering of lymphocytes about tumor cells, appeared to correlate with the extent of nodal metastasis and was noted in 10 cases of uninvolved nodes, and in none of 4 cases with extensive involvement.

Ambus and associates[1] compared the immunologic responses of axillary node lymphocytes with those from peripheral blood. Lymphocytes from 10 patients with Stages III and IV breast tumors were studied in a lymphocyte transformation assay using autologous breast tumor cells as a source of stimulation. Regional node lymphocytes gave higher responses than those of peripheral blood, which suggested to the authors that even in advanced breast cancer, regional nodes were still immunologically active. A similar study comparing regional nodes and peripheral blood lymphocytes was carried out by Ellis et al.[11] in 24 patients with Stage I breast tumors. Activity was determined by a leukocyte migration assay employing a homologous breast tumor extract. Control lymphocytes, obtained from 10 patients with non-neoplastic disease did not show reactivity whether from blood or lymph nodes. In the cancer patients, Ellis' findings supported those of Ambus: positive reactions were more frequently seen with regional node lymphocytes than with those from peripheral blood.

Tsakraklides et al.,[32] in a study of 81 patients, attempted to correlate PHA response and T and B cell content with histologic pattern of regional nodes. Increased T cell and PHA values and decreased B cells were associated with a pattern of lymphocyte predominance, whereas the reverse findings were associated with a germinal center predominance. Involved nodes were also observed to have fewer T cells and increased B cells. No control lymph nodes were included in this study, however.

Immunologic Responses and Tumor Components

Immunologic assays have been applied to human breast cancer in the hope of demonstrating an immunologic facet to the disease and also of providing a source of clinically relevant data. The "specificity" of immunologic responses observed in many studies has not been determined and, indeed, the clinical significance of "response" versus "no response" has received little attention. The presence of anti-tumor

antibody has been examined by immunofluorescence,[40] immunodiffusion,[20] and complement fixation[20] studies of patients' sera. Although antibody has been noted in several papers, the specificity and clinical relevance are not clarified.

Cell-mediated immunity has been examined by in vivo and in vitro methods. Stewart and Orizaga[48] skin tested 56 patients with extracts of their own tumors, and suggested that delayed hypersensitivity reactions observed in 12 patients correlated with the presence of anaplastic tumors, regional node metastases, mononuclear cell infiltrates, and poor survival. Black and Leis,[4] on the other hand, using a skin-window technique, found cellular reactivity more frequent in noninvasive or in situ carcinoma than in invasive disease.

In vitro methods of evaluating cellular immunity to breast cancer have included assays for lymphocyte tumor-directed cytotoxicity, lymphocyte transformation stimulated by tumor cells, and inhibition of leukocyte migration or adherence in the presence of tumor extracts. The cytotoxicity assay has dropped from use mainly because a high degree of nonspecific cytotoxicity has been observed with lymphocytes from virtually all individuals whether tumor-bearing or not.[17] At present, the significance of such findings is not clear. The leukocyte migration assay has also been used extensively in human breast cancer studies. Association of migration inhibition activity with clinical status was suggested by Black et al.,[5] who observed the frequency of positive tests to autologous tumor extracts in the order of in situ > Stage I > Stage II. No reactivity was obtained with extracts of normal breast tissue. Brandes and Goldenberg[6] reported that migration inhibition tests to a battery of homologous breast tumor extracts were more often positive among patients in remission than among those in relapse or normal controls. In a horizontal study of 57 patients post mastectomy, the follow-up period was insufficient to allow any conclusions to be drawn.

An assay involving inhibition of peripheral blood leukocyte adherence to glass by tumor extracts has been tested in breast cancer. Fujisawa et al.[14] examined activity of 66 patients, with controls consisting of 23 patients with other tumors and 39 normal individuals. Reactivity to a breast carcinoma extract was demonstrated by 63 per cent of patients with breast tumors, but by only 16 per cent of patients with other diseases, and by 7 per cent of normal controls. These authors found no difference in reactivity according to staging of patients or in long-term survivors (>5 years) versus patients with recurrent disease. In contrast, Flores et al.[13] found significant differences in leukocyte adherence inhibition among a group of 360 patients with breast carcinoma tested before surgery. The frequency of positive responses was stage-related, with 85 per cent reactivity in Stages I and II, 45 per cent in Stage III, and 29 per cent in Stage IV. At 18 months after surgery, responses disappeared in patients with no evident disease, whereas those with recurrence demonstrated positive tests. Clinical significance of leukocyte migration or adherence inhibition assays requires further clarification.

IMMUNOTHERAPY

Immunotherapy, a relatively recent addition to treatment of cancer, may be generally classified as passive and active-specific or nonspecific. Passive immunotherapy refers to approaches in which the patient is given immunologic reagents thought to have anti-tumor capability. Such reagents may consist of whole lymphoid cells, sera, or lymphoid cell products such as transfer factor or "immune" RNA. In active specific immunotherapy, the host is stimulated by administration of tumor antigens to mount an immune response that specifically causes tumor cell death. Nonspecific immunotherapy used in most clinical trials consist of administration of agents such as Bacille Calmette-Guerin (BCG), *Corynebacterium parvum (C. parvum)*, a methanol extractable residue of BCG (MER), or levamisole.

Passive Immunotherapy

Pilch and associates[38] have reported on studies in progress using "immune" RNA in treatment of human cancer, including breast carcinoma. This reagent was prepared by extracting RNA from the lymphoid organs of sheep that had previously been immunized to various human tumors. Although the study was too preliminary for any conclusions to be made, the investigators reported "immune" RNA to be nonimmunogenic and nontoxic, favoring continued human use.

Another approach to passive immunotherapy has been the administration of transfer factor, a 2000 to 3000 molecular weight molecule that is insensitive to RNase or DNase and is nonimmunogenic. The injection of transfer factor extracted from leukocytes of a donor sensitized to a known antigen, such as PPD, has been shown to confer such sensitivity upon the recipient whose skin test then reverts to positive.[35] Transfer factor for clinical use in breast cancer has been obtained from leukocytes of healthy, adult donors but, unfortunately, has not been shown to be promising by Oettgen et al.[35] or by LoBuglio and Neidhart.[26] Our experiences with transfer factor, although in melanoma and hypernephroma, have also been unrewarding.[7]

Active-Nonspecific Immunotherapy

In nonspecific immunotherapy, reagents employed exert an "adjuvant" effect which can be defined as the ability to nonspecifically enhance the immune response to a variety of antigens. One such agent is *C. parvum*, a killed bacterial vaccine that has been shown to prolong survival in patients with advanced breast cancer. In one clinical trial by Israël,[22] 82 patients received conventional chemotherapy every two weeks, and then were randomized so that 39 continued to receive chemotherapy alone, and 43 received chemotherapy plus 4 mg of *C. parvum* subcutaneously per week. Survival for up to three years was significantly prolonged in the group treated with *C. parvum* compared with the group treated conventionally. In another study in which *C. parvum* was administered intravenously to patients with a variety of metastatic cancers,[21] partial responses were observed in 9 of

33 patients, including 3 of 6 patients with breast cancer. Haskell et al.[16] described a small trial with intravenous *C. parvum* accompanying conventional chemotherapy in 14 patients with metastatic breast carcinoma. Unfortunately, these investigators reported severe toxicity and a poor response rate with *C. parvum*. Chemotherapy was also combined with treatment with *C. parvum* by Pinsky and associates,[39] who noted enhanced survival in patients treated with *C. parvum* compared with the control chemotherapy group, although differences were not statistically significant. *C. parvum* was administered by injection of 4 mg subcutaneously per week following the method of Israël.[22]

Levamisole, another nonspecific potentiator of the immune response, is a synthetic, antihelminth drug. A clinical trial of levamisole in Stage III breast cancer was performed by Rojas et al.[42] All 43 patients entered into the study had previously received radiotherapy to the breast, axilla, and supraclavicular areas. The survival rate at 30 months was 90 per cent for 20 patients receiving oral levamisole compared with 35 per cent of the 23 control patients.

Treatment with BCG, an attenuated strain of *Mycobacterium bovis*, has been reported by Gutterman et al.[15] to enhance survival in a group of patients with Stage IV breast cancer receiving chemotherapy plus BCG when compared with a control group receiving only chemotherapy. Repeated doses of Tice strain, lyophilized BCG, were given by scarification of the arms and thighs. Inclusion of BCG in a chemotherapy program for Stage II breast cancer was also described by Buzdar et al.,[8] who noted that at 32 months of study, 5.3 per cent of patients treated with BCG had relapsed compared with 40 per cent of historical controls. A nonviable methanol extractable residue (MER) of BCG was incorporated into a chemotherapy protocol for Stage II breast cancer by Perloff et al.,[37] but at 30 months of study, MER was not shown to offer any clinical advantage. Sparks and associates[44] have described two therapy trials in breast carcinoma employing BCG. In one study, 11 women with recurrent disease in the chest wall received injections of BCG into the tumor nodules. Six patients responded and became disease-free in the chest area and one patient had a partial response. In another clinical study by Sparks et al.,[44] specific and nonspecific immunotherapy was incorporated into a chemotherapy regimen, and patient groups were treated with chemotherapy alone, chemoimmunotherapy (BCG), or chemoimmunotherapy plus injection of lethally irradiated homologous tumor cells. No conclusive data are yet available.

SUMMARY

Although our knowledge of immunologic processes in breast cancer is still inadequate, many preliminary studies described here may yield valuable information after long-term patient follow-up. At present, there is no specific tumor marker diagnostic of breast cancer, but markers such as CEA, ferritin, immune complexes, and especially estrogen receptors have strong potential as prognostic indicators. As a

group, breast cancer patients, as do those with other malignancies, demonstrate reduced immunologic capacity, therefore assays of nonspecific immune function may not be relevant. Assays of "specific" reactivity to breast tumor antigens, however, warrant further investigation as clinical tools. Application of immunotherapy to breast cancer is relatively recent and few trials have more than preliminary data. Determination of estrogen receptors should be included in future clinical immunotherapy protocols so that true evaluation of immunologic responses may benefit, hopefully, from our awareness of the endocrine milieu.

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The Pathologist's Role in the Diagnosis and Treatment of Invasive Breast Cancer

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John Adams, the second president of the United States, proclaimed that if change is not necessary then it is necessary not to change. Although this precept was undoubtedly intended as governmental policy, it would appear to have its corollary in the surgical management of breast cancer. One operation, the radical mastectomy, was practiced without significant challenge for at least 65 years. Yet, that change might be necessary was prompted by the realization that the survival rate was little altered during that period. More recent advances in the understanding of the biologic nature of cancer, particularly in regard to its systemic dissemination, coupled with the desirability of a more cosmetically acceptable result have led to the reevaluation of the surgical management of patients with breast cancer. As a consequence, largely if not entirely due to the result of prospective clinical trials and the thought provoking polemics engendered by their initiation and findings, it is becoming more evident that treatment modalities for this disease may be more individualized than heretofore appreciated.

If treatment is to be individualized it becomes apparent that the pathologist's role in this regard must be more sophisticated than in the past, requiring him to provide more information than simply whether a lesion is "benign or malignant" as has been customary in the past. Pathologists as well as surgeons, oncologists, and radiotherapists must be aware of those characteristics of the tumor and patient which may influence survival and therefore the selection of appropriate therapy. Similarly, it should be appreciated that a meaningful pathologic assessment of specimens of breast cancer may require more time and consideration than is attendant with the customary, conventional approach of surgical treatment characterized by almost simultaneous biopsy-frozen section-operative intervention.

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Supported by USPHS Grant CA-12027 and Contract NOI-CB 23876 (Breast Cancer Task Force).

During the past seven years we have been engaged in the pathologic evaluation of material from 1539 patients with invasive operable breast cancer who were entered in the National Surgical Adjuvant Breast Project (NSABP) Protocol No. 4 during the period from 1971 to 1974. These women had been prospectively randomized so that those with clinically negative axillae were treated by (1) radical mastectomy (333 patients) or (2) total mastectomy with (330 patients) and (3) without (334 patients) postoperative irradiation. Those with clinically positive axillae received either (1) radical mastectomy (265 patients) or (2) total mastectomy and irradiation (277 patients). Outcome has been measured by treatment failure which is defined as the time from treatment to the first evidence of local or regional recurrence or systemic metastases. This may be expressed as treatment failure rate (per cent of failure per average months at risk). The average period of follow-up for all cases in this analysis was 54 months. Noteworthy has been the failure thus far to discern any statistically significant differences in the treatment failure rates in the various subsets of patients with clinically negative axilla: (1) 23 per cent, (2) 22 per cent, and (3) 28 per cent, respectively; or those in the two subsets of treatment for clinically positive axillae: (1) 39 per cent and (2) 42 per cent respectively.

The relation between treatment failure and 34 pathologic features of these cases was studied utilizing contingency table analyses. In some instances observations were not possible for all of these parameters in all of the 1539 cases. These exceptions shall be noted. Associations with a P value of .05 or less were regarded as statistically significant. Their definition and description have been noted in detail in previous communications.[30, 32, 34] Reference shall also be made to some studies based upon the author's own material, which despite their retrospective nature, establish additional discriminants or provide insight into those obtained from the NSABP material.

Tumor Border

It has been suggested on the basis of retrospective pathologic data and more recent mammographic study[41] that the incidence of axillary nodal involvement is less and 5 year survival greater[22, 52] in patients whose tumors are circumscribed as opposed to those in whom these lesions have an irregular or infiltrative border. Some have failed to find any relationship between configuration of the tumor border and survival.[2] Silverberg and associates[65] also found no difference in survival between patients whose tumors were or were not circumscribed, but that if the mucinous and medullary forms of cancer were deleted from the circumscribed group, the prognosis of the latter was actually worse. However, in our material gross (P = .003) as well as microscopic (P = .024) circumscription of the dominant mass was associated with less frequent treatment failure than when the lesions were stellate or infiltrative. Surprisingly, the incidence of circumscribed tumors was similar when assessed grossly (25 per cent) or microscopically (24 per cent).

Tumor Size

Assessment of tumor size appears to represent an obvious discriminant for the prognosis of mammary cancer. The efforts devoted to the "early" detection of breast cancer as well as the designation of minimal cancer for those lesions measuring less than 5 mm, and the recognition that almost three-fourths of the patients with tumors larger than 5 cm have nodal metastases when first examined conveys the prognostic importance of tumor size. Indeed, some studies have disclosed a direct relationship between tumor size and survival.[15, 24] Yet, on the other hand, others have failed to observe such a relationship.[44] The reasons for such a dichotomy of findings is not totally clear, although as with most retrospective analyses different stages of disease or treatments are often analysed collectively. An appreciation of the various histologic types and grades of malignancy of cancers appear to be sufficient to recognize that the doubling times or growth rates of all breast cancers may not be similar. As an example, Bloom[14] could find no correlation between tumor size and prognosis in those cancers regarded as being of low or high degrees of malignancy, although a poor prognosis was encountered in patients with lesions greater than 2 cm that were of an intermediate grade of malignancy. Fisher and associates[27] observed poorer survival with large tumors when more than three axillary nodes exhibited metastases than when no nodes or one to three nodes were involved. No difference in survival was encountered in patients with large or small tumors in whom no nodes or one to three nodes were involved. All of this information suggests that tumor size may represent a significant, albeit not independent, discriminant.

Our own studies indicate a consistent correlation between tumor size, when expressed as greatest diameter by pathologic measurement, and treatment failure rate. Tumors > 5 cm had a higher incidence of treatment failure than those measuring 2.1 to 5.0 cm, which in turn had a greater failure rate than those measuring ≤ 2.0 cm ($P < .00005$). The median size of 3.0 cm encountered in our study coincides with that recorded for the period of 1948 to 1968 by Cady,[18] suggesting that there has been no greater increase in the detection of smaller tumors during the past two and a half decades. It should be noted that our data were not collected from women enrolled in a mass screening survey utilizing mammography. It appears reasonable to assume that the latter may result in the detection of smaller tumors, although firm evidence in support of such a contention or the enhancement of survival attendant with such detection remains to be presented.

Histologic Tumor Type

It is not uncommonly held that the determination of histologic type of breast cancer may represent a useless exercise despite some information to the contrary.[16, 17, 19, 46, 60, 68] Unfortunately, pathologists are often confused and uncomfortable with this aspect of the examination. This appears to be the result of the many terminologies and classifica-

tions extant for this purpose as well as the complex appearance of many breast cancers resulting from their intraductal component. Confusion is also added by those classifications that appear to reflect both descriptive terminology as well as estimates of degree of malignancy. We have found a simple listing of histopathologic type or types based principally on growth pattern and/or special histopathologic features of the *invasive* component to be highly practical, inclusive, and reproducible.[30] In our scheme a separate assessment of the intraductal component is made (vide infra). The degree of malignancy appears to be more appropriately represented by nuclear and histologic grades. The following represents prototypes that may be encountered in pure or combination forms.

INFILTRATING DUCTAL NOS CARCINOMA. The infiltrating ductal carcinoma without special features, or not otherwise specified (NOS), is the most common histologic type, comprising approximately 50 per cent of all breast cancers. Histologically, it appears as groups of cells varying in size and stromal content (Fig. 1*A*). Although by light microscopy the cells lack any special features, it should be noted that electron microscopy often reveals such elements to contain intracyto-

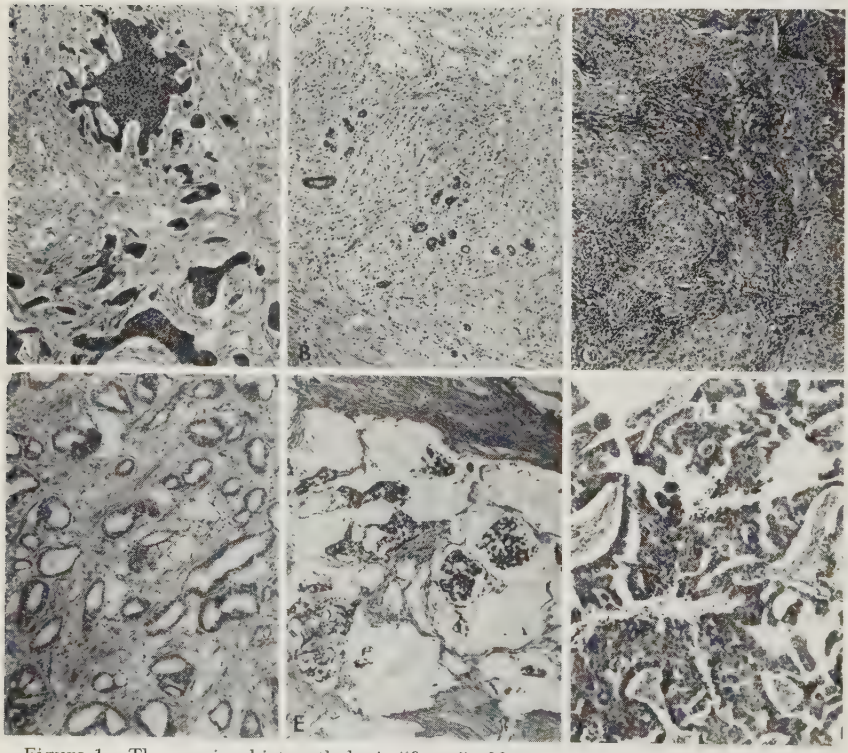

Figure 1. The varying histopathologic "faces" of breast cancer are: *A*, NOS variant; *B*, lobular invasive; *C*, medullary; *D*, tubular; *E*, mucinous; and *F*, papillary. (Hematoxylin and eosin stain, × 100.)

plasmic lumens or evidence of some degree of differentiation.[28] Nevertheless, until distinguishing characteristics are recognized which might provide criteria allowing for the subdivision of this group, the NOS designation appears to be most appropriate and pragmatic. The NOS histologic type has been found to be associated with the greatest incidence of treatment failure among the "pure" types or combination tumors (Table 1).

LOBULAR INVASIVE CARCINOMA. Next in frequency of treatment failure is the lobular invasive cancer. Its histologic appearance is quite distinctive, being characterized by the presence of small sometimes innocuous-appearing neoplastic cells disposed singly or at most in small clusters in an "Indian file" or targetoid pattern often about neoplastic or non-neoplastic ducts (Fig. 1*B*).[29, 40, 54, 56, 58] The presence of skip areas within the breast parenchyma signifies its atavistic lobular derivation. It is highly suspect that most, if not all, scirrhous carcinomas of older terminologies represent examples of this histologic type. It should be noted that on occasion the cells comprising lobular invasive cancer may exhibit a signet ring appearance due to their mucin content or such cells may be arranged in small tubules, the so-called tubulo-lobular invasive cancer.[33] Also, and less commonly, the tumor cells may appear, at least in some foci, as larger aggregates comprising the so-called small cell or lymphomatoid carcinoma. Nevertheless, the classical arrangement of lobular invasive carcinoma is usually evident, warranting the conclusion that these rarer forms do indeed represent variants of lobular invasive cancer. It should be emphasized that in our experience foci of in situ lobular carcinoma may or may not be evident in sections from these tumors. Also the presence of in situ lobular carcinoma is not invariably found to be accompanied by the invasive form but with other histologic types. Thus, although it is common practice to accept the view that lobular invasive cancer arises from its in situ analog, such a relationship does not appear to be restricted to this histologic tumor type.

MEDULLARY CARCINOMA. The medullary cancer has been often regarded as a prognostically favorable form of breast cancer, at least on the basis of retrospective studies. However, as indicated in Table 1,

Table 1. *Incidence and Treatment Failure of Principal Histologic Types of Breast Cancer*

HISTOLOGIC TYPE	TREATMENT FAILURE		TOTAL
	Yes	No	
Infiltrating duct NOS	287 (36.1%)	508 (63.9%)	795 (50.3%)
Lobular invasive	25 (29.1%)	61 (70.9%)	86 (5.4%)
Medullary	21 (26.9%)	57 (73.1%)	78 (4.9%)
Mucinous	0 (0%)	35 (100%)	35 (2.2%)
Tubular	1 (6.7%)	14 (93.3%)	15 (0.9%)
Combinations	143 (25.0%)	428 (75%)	571 (36.1%)
TOTAL	477 (30.2%)	1103 (69.8%)	1580 (100%)

our own material fails to reflect such a favorable position for this tumor type. It is only slightly better than the lobular invasive type, apparently being intermediate in prognosis. The tumor in its classical presentation exhibits circumscription of aggregates of large, polygonal neoplastic cells with dedifferentiated nuclei and prominent nucleoli (Fig. 1*C*). The stroma contains scant fibrous elements but numerous lymphocytes and plasma cells. Indeed, this cellular stromal infiltrate together with the purportedly good prognosis of this tumor type has undoubtedly led to the somewhat teleological deduction that the lymphoid reaction represents a favorable host response.[8, 11, 13, 43] Not only have we failed to find this tumor type to be associated with a good prognosis, but also the presence of a cellular infiltration in breast cancer does not appear to be consistent or clearly related to treatment failure. During the course of our studies we encountered some cancers that had the appearance of medullary cancer, although they lacked one of their criteria such as circumscription, cellular infiltrate, or anaplastic nuclei. Such neoplasms were tentatively regarded as atypical medullary forms.[1] Despite this aberrant histologic presentation we have found their treatment failure rate to coincide with that of the classical medullary type and therefore now include such lesions in the medullary group.

COMBINATION TUMORS. Also intermediate in prognosis are the combination tumors, the most common of which are the NOS and tubular and NOS and lobular invasive mixtures.

TUBULAR AND MUCINOUS CARCINOMA. The most favorable histologic types of breast cancer when found in pure forms are the tubular and mucinous variants. So-called tubular carcinoma exhibits a failure rate that is only slightly greater than that observed with mucinous cancer of the breast. Unfortunately, they constitute only 1.2 and 2.4 per cent of all breast cancers respectively. The tubular carcinoma may superficially mimic sclerosing or blunt duct adenosis and is not infrequently "underdiagnosed" because of this similarity. It is comprised of tubular structures that are typically lined by a single layer of well differentiated epithelium (Fig. 1*D*). They lack basement membrane by conventional light as well as electron microscopic examination. The surrounding stroma is abundant and may exhibit fluorescence after congo red staining and/or aggregates of elastic fibers. The tubular carcinoma frequently is associated with an intraductal component exhibiting an adenocystic configuration, and invasive foci of this latter may be found associated with the tubular elements. A purely invasive adenocystic pattern is another rarity comprising less than 0.5% of all breast cancers. Although originally we regarded this form as being distinct from the tubular type, the great overlapping of the two patterns as well as the similarly good prognosis putatively regarded to obtain with adenocystic carcinoma has prompted us to include this tumor type in the tubular group.

The appearance of the mucinous cancer of the breast is familiar to most pathologists, being characterized by aggregates of usually well differentiated cells arranged in solid masses, tubules, or papillary configurations within pools of mucin (Fig. 1*E*). Its border is usually of the

pushing or circumscribed type. No treatment failures have been observed thus far in patients with mucinous cancers (Table 1). It should be noted that the prognosis of patients with combination mucinous tumors is less favorable. No mention of the papillary cancer has been made (Fig. 1*F*). Our material contains too few examples to allow for any statements regarding its clinical behavior. The papillary pattern is occasionally found in combination with other types. Its prognosis in that situation is similar to that of other combination tumor types.

Nuclear Grade

That the degree of nuclear atypia might be a reliable index of prognosis of breast cancer has been emphasized by Black and associates.[8, 9, 11, 13] Yet, some have found the method to be of limited[68] or no[50] value in this regard. After some experience the grading of nuclei is relatively simple and quite reproducible. It is unfortunate, however, that the scale employed for nuclear grading is converse to that customarily employed for the evaluation of differentiation such as in histologic grading (vide infra). We have employed a modification of the system utilized by Black and associates[9] in which their grades 0 and 1 are combined and represented by nuclear pleomorphism, large size, prominent nucleoli, and frequent mitoses; grade 2 nuclei are intermediate and those of grade 3 are well differentiated, closely simulating the nuclei of non-neoplastic ductal epithelium. A consistent relationship between nuclear grade and treatment failure rate was observed in our material, with the greatest incidence occurring with tumors exhibiting grade 1 nuclei and the least with those regarded as grade 3. Tumors with grade 2 nuclei were intermediate ($P = .005$).

Histologic Grade

The degree of malignancy of breast cancers may be expressed as its histologic grade. Although there have been several schemes devised for such assessment, all incorporate the degree of tubule formation and nuclear atpyia. In order to circumvent the somewhat tedious and time consuming method of individually scoring numbers of mitoses, nuclear regularity, and so forth, we have devised a simple method of grading which utilizes nuclear grade and tubule formation as depicted in Table 2. It is not surprising that, as with nuclear grade, there is a consistent relationship between histologic grade and treatment failure rate, with the latter being greater in tumors designated as histologic grade 3 than in those regarded as grade 2, which in turn is greater than tumors designated as grade 1 ($P < .00005$). Again, as with nuclear grade, the incidence of histologic grade 1 tumors is quite small being only 2.5 per cent, whereas approximately two-thirds of breast cancers are regarded as being the most malignant histologic grade.

Blood Vessel Invasion

There have been relatively few reports concerning the incidence and possible signficance of blood vessel invasion in breast cancer. Results reveal an incidence of such an event to vary from 21 to 46 per

Table 2. *Scheme of Histologic Grading and Its Relationship to Treatment Failure*

TUBULE FORMATION*	NUCLEAR GRADE	HISTOLOGIC GRADE	TREATMENT FAILURE		TOTAL
			Yes	No	
Pure, in part	3	1	6 (12.5%)	42 (87.5%)	48 (3.1%)
Pure, in part	1,2	2	112 (23.8%)	358 (76.2%)	470 (30%)
Absent	3	2			
Absent	1,2	3	357 (34.1%)	690 (65.9%)	1047 (66.9%)
TOTAL			457 (30.4%)	1090 (69.6%)	1565 (100%)

*Also including adenocystic.

cent.[5, 39, 49, 63] It is our impression that such histologic estimates of the incidence of blood vessel invasion are inordinately high. This appears to be related to the difficulty in distinguishing between true vascular extension and intraductal involvement. Recourse to elastic tissue stains does not totally resolve the problem since both ducts and blood vessels may contain an elastic mantle, although it is true that with some experience the deposition of such fibers in these structures may be delineated. Dependence solely upon elastic tissue stains for the demonstration of vascular extension may result in an oversight of this phenomenon in blood vessels of small caliber which lack a distinctive elastic layer. We have found vascular extension in 4.3 per cent of our cases of invasive breast cancer. That this may represent an underestimate of the actual incidence of venous tumor emboli is suggested by the recent study of Golinger, Gregorio, and Fisher,[42] who identified tumor cells in mammary vein blood of 26 per cent of patients with Stages I and II disease undergoing total mastectomy and axillary dissection. Disparity between circulating tumor cells and the histopathologic demonstration of venous extension is similar to our experience in a similarly designed study of colorectal carcinoma.[38] The biological significance of these blood borne tumor cells is still unknown, and if it is comparable to that in colorectal cancer, may not be prognostically important.[25] Nevertheless, treatment failure rate has been found to be significantly greater in patients in whom histopathologic evidence of venous extension is found than in those in whom this feature is lacking ($P < .00005$).

Lymphatic Extension

Extension of carcinoma into lymphatic channels within or in close proximity of the dominant mass has been observed in approximately one-third of our cases and has been regarded as questionable in another one-fourth. This latter designation is used for the citation of tumor aggregates in tissue spaces in which identification of an endothelial lining is equivocal. Treatment failure was found to be significantly ($P < .00005$) greater when such lymphatic extension was present than in its absence or when judged to be questionable. There was no difference in treatment failure rates in those without demonstrable lym-

phatic extension or in those in whom it was assessed as questionable. This relationship between intralymphatic extension and treatment failure appears to be applicable only to patients with axillary nodal metastases (Stage II) (vide infra).

One of the dilemmas confronting those concerned with the treatment of patients with breast cancer is the decision whether to administer chemotherapeutic or other adjunctive measures in patients with pathologic Stage I disease who would not be otherwise considered as candidates for such therapy but in whom pathologic examination has disclosed lymphatic extension within the dominant mass or its immediate vicinity. Nime and associates[59] recently have reported the incidence of distant metastases to be greater in patients designated as having Stage I disease with intralymphatic tumor emboli than in those lacking this finding. This has led to the consideration that this subset of patients with Stage I disease should receive adjunctive therapy. Yet, it is noteworthy that the number of cases upon which this conclusion was based was few,[15] and more importantly the authors made no distinction between lymphatic extension in the immediate vicinity of the cancer or lymphatic tumor emboli in portions of the breast remote from the dominant mass. We have found the latter occurrence to be associated with a high rate of treatment failure.

However, in our experience the presence of "multicentric lymphatic tumor emboli" almost invariably occurs in patients with clinical as well as pathologic Stage II disease and other ominous pathologic characteristics including microscopic skin involvement.[30] Such cases present the pathologic characteristics observed in so-called inflammatory cancer, although many of the patients do not exhibit clinical features of the latter. Analysis of the significance of lymphatic extension within or immediately about the dominant mass in patients with pathologically proven Stage I disease has failed to reveal any association between this phenomenon and treatment failure. Lastly, as will be noted, there does not appear to be any difference in treatment failure rates in patients in whom routine pathologic examination and those in whom an extended pathologic study of the regional nodes uncovers occult metastases. Thus, the weight of evidence would suggest that the pathologic demonstration of intralymphatic extension within or immediately about the dominant mass in patients with Stage I disease does not, as yet, warrant the administration of adjunctive therapy if this latter is inappropriate, as is now believed, for such patients.

Mucin

The results of some early[21, 53] as well as more recent[67] investigations have suggested that mucin content may represent one of the most significant prognostic indices in breast cancer, although this has been disputed by others. It will be recalled that the pure mucinous carcinoma of the breast has the best prognosis of all histologic types. We agree with Hamlin's conclusion that the presence of mucin represents another indicator of neoplastic differentiation.[43] One-half of all of the cancers in our material contained some degree of mucin. Further, treatment failure was significantly less when mucin was considered to

be present in moderate or marked amounts than when it was categorized as being slight or absent ($P < .00005$).

Tumor Necrosis

Although tumor necrosis would appear, because of its obvious importance in the net rate of tumor growth, to be an important discriminant in breast cancer, little attention has been directed to its possible significance in this regard. We have found tumor necrosis to be present in approximately two-thirds of all breast cancers. Moderate or marked degrees of necrosis, particularly that of the non-comedo or infarct type, was found to be positively correlated with treatment failure ($P = .002$).[35] This finding is somewhat paradoxical since it might be suspected that the growth rate of tumors exhibiting necrosis would be decreased. Yet, multivariate analysis has revealed necrosis to be related to treatment failure independently of tumor size or nodal status.[35] This alteration might be a reflection of differentiation even though its effect in relation to treatment failure was found to be independent of it in those tumors of most malignant histologic grade.

Type of Intraductal Component

It will be recalled that in our scheme of histologic typing of breast cancers attention is directed to the invasive rather than intraductal component of the tumor. Yet, our data do reveal that the type of intraductal component present may play a prognostic role. Indeed, the treatment failure rate appears to be greater in tumors whose intraductal component is of the comedo type than when it is solid. It is also more frequent with this latter pattern than when it appears as papillary or adenocystic configurations ($P = .002$).

Nipple and Skin Involvement

Histologic study of the skin overlying the dominant mass or of the nipple of the breast is unfortunately often overlooked in the examination of breast specimens. Yet, as might be expected, the presence of involvement of these structures is accompanied by a high frequency of treatment failure ($P = .002$ for nipple and .006 for skin). Instances of such involvement would qualify such cases as examples of Stage III disease. It should be noted, however, that Paget's disease per se (nipple involvement characterized by intraepidermal deposits of neoplastic cells) does not appear to have any greater incidence of treatment failure than when these epidermal changes in the nipple are lacking. Thus it is the lymphatic and ductal extension into the nipple that are ominous.

Lymph Node Status

It has long been recognized that the prognosis in breast cancer is to a large degree dependent upon the clinical and pathological assessment of the regional or axillary lymph nodes. Despite an overall error of 32 per cent in the clinical assessment of the axillary nodes (24 per cent false positive, 39 per cent false negative); patients with clinical Stage II disease do exhibit a greater incidence of treatment failure

than those assessed as clinical Stage I ($P < .00005$). Contrary to the experience of others,[20] we have not found any prognostic advantage when the nodes are found to be clinically positive but pathologically negative.

The results of this present analysis confirm previous findings that treatment failure is more significantly related to the number of nodes positive for metastases than to the proportion of involved nodes.[29] Treatment failure was least in those in whom no nodes exhibited metastases (12 per cent); greater when there were one to three positive nodes (28 per cent); and greatest in those in whom four or more positive nodes were encountered (60 per cent). Since survival is not universal in patients with negative axillary nodes, it may be cogently inquired whether an extended pathologic examination of axillae judged to be negative by routine pathologic study might not disclose metastases. Information in this regard assumes not only practical pathologic but also therapeutic significance since the decision for the administration of chemotherapeutic agents is, at least at present, dependent upon the presence or absence of nodal metastases.

Some limited investigations of this problem have been attempted by studying serial sections of axillary lymph nodes found to be negative by routine examination (the study of one section prepared from one block of a hemi-transected node). Saphir and Amromin[64] detected "obscure" metastases in 10 of 30 cases examined by the extended method. Pickren[61] performed a similar study of 51 patients with presumably negative nodes and found 22 per cent of these to be positive after the study of serial sections. In a recent study of similar nature from our own hospital material,[37] occult nodal metastases were found in 24 per cent of 78 patients studied. Since there was no difference in 5 year survival between those with and without these occult metastases, it was suggested that such patients might qualify as representing Stage 1½ disease. It was also concluded, undoubtedly to the pleasure of practicing pathologists, that the extended histopathologic method of nodal examination was more academic than practical or therapeutically significant.

These findings are also germane to considerations concerning the possible prognostic significance of the demonstration of intralymphatic extension in tumors of Stage I patients alluded to above. Most of the occult metastases detected by semi-serial sections were in the form of emboli within capsular or subcapsular lymphatic sinuses of these lymph nodes. Yet, as indicated, survival was unaffected by their presence. Further, the presence of occult metastases was not statistically related to intralymphatic extension within the dominant mass. Indeed, we could not find any pathologic discriminants in our material which appeared to be related to treatment failure in patients with Stage I disease.

Since the occult metastases that measured ≤ 1.3 mm did not influence survival, the possibility that the size of the metastases might represent an important discriminant for breast cancer was considered. It had been noted previously by Huvos and associates[47] that the 8 year survival rate was comparable for patients whose axillary metastases

measured less than 2 mm (micrometastases) in level 1 nodes and those in whom routine pathologic examination failed to reveal any nodal metastases. This relationship in these patients was confirmed by Attiyeh and associates[4] after a 14 year period of observation. However, they noted that patients with micrometastases who survived had only one to three positive nodes, whereas those with macrometastases (≥2 mm) and a worse prognosis had four or more positive nodes.

Our own analysis of NSABP material revealed that survival, but not treatment failure rates, were comparable for patients with micrometastases and those without such lesions. On the other hand, treatment failure rates were comparable for those with micro- and macrometastases which, as expected, were significantly greater than in those lacking metastases. Multivariate analysis disclosed that the apparent effects on survival of metastases were more directly related to the number of nodes involved rather than to the size of metastases, as suggested by Attiyeh and associates.[4] Yet, a subset of patients with micrometastases that measured ≤ 1.3 mm was identified which exhibited survival and treatment failure similar to those of the negative node patients.[36] This effect was unrelated to the number of nodes involved. This information reaffirms our conclusions noted above regarding occult metastases and supports the view suggesting that there may be a group of patients that can be appropriately regarded as Stage 1½.

We have not attempted to localize the level of nodal involvement in those cases in which radical mastectomy was performed, since such evaluation was not commonly employed by pathologists contributing their material to the NSABP cooperative study. Crude and relative 5 and 20 year survivals have been reported to be inversely proportional to the level of nodal involvement.[55] However, more recent examination of the prognostic significance of level of node involvement by Smith and associates[66] indicates that such estimates are preempted by estimation of the number of nodes involved. Similarly, there is apparently no greater prognostic information to be found by examination of the interpectoral or Rotter's nodes according to Kay[48] or the internal mammary chain as reported by Donegan[23] than by that provided by study of the regional or axillary nodes. It is now generally recognized that axillary nodal involvement, aside from that of the occult type indicated above, appears to represent a satisfactory indicator of the likelihood of systemic disease in breast cancer.

There is experimental evidence that the regional lymph nodes play a significant role in tumor immunity. Some investigators[3, 7, 10, 12, 70] have reported a more or less direct relationship between survival and sinus histiocytosis of regional lymph nodes. All have considered this reaction to be a manifestation of the host response, vis á vis immunologic reaction to tumor growth. On the other hand, others[6, 50, 57] have failed to confirm this relationship of sinus histiocytosis to survival. Further, we can find no evidence to unequivocally indicate that sinus histiocytosis does indeed represent an immunologic reaction. Although an earlier appraisal of our material suggested that the absence of sinus histiocytosis was related to short-term treatment failure (1 year),[1] our more

recent analysis fails to reveal any clear or unequivocal association between sinus histiocytosis and treatment failure. Thus, at least at present, we look upon the prognostic significance of sinus histiocytosis with some degree of skepticism.

More recently, Tsakrakildes and associates[69] correlated 5 and 10 year survivals in a group of 227 women with breast cancer with nodal morphologic features other than sinus histiocytosis which were considered to reflect immunologic function. They found nodes exhibiting a lymphocyte predominance pattern which was connoted with T cell hyperplasia to be associated with a high survival rate, whereas a lymphocyte depleted appearance indicated a poor prognosis. Predominance of germinal centers or unstimulated patterns were found in those with intermediate survival. The former has been regarded to reflect humoral antibody formation. In an earlier study we observed a number of associations with the various nodal patterns but no relationship to short-term treatment failure (3 to 4 years).[32] However, our most recent analysis of the data indicates that the germinal center pattern is indeed associated with a greater incidence of treatment failure than that observed in patients with other nodal appearances. A similar relationship between this pattern of lymph node change and survival has been recently recorded in a much smaller series of patients by Hunter and associates.[45] The relationship between treatment failure and germinal center hyperplasia of lymph nodes is of interest since it suggests that humoral antibody formation may have an adverse effect upon the natural history of breast cancer. Such a view of course is in accord with the proposed action of "blocking" humoral antibodies.

It is well appreciated that the nodal metastases may appear to be confined within the capsule of the node in some instances, whereas in others extension into the perinodal tissue is evident. A previous report relating the influence of extranodal extension of axillary metastases on treatment failure revealed the latter to be significantly increased at 2 years following operation.[34] This observation was confirmed for the longer period of follow-up upon which this presentation is based ($P = .002$).

Lipid Content

There have been surprisingly few histochemical studies of breast cancers. Most of these have been concerned with the glycogen content of the tumor cells, which incidentally our analyses indicate has no effect on prognosis. Relatively little information concerning intracellular lipid in the cancer cells is available except for several reports characterizing a so-called lipid rich cancer that has been purported to be a unique variant of breast cancer.[1, 62] In our own hospital material we have found intracytoplasmic lipid in two-thirds of 87 consecutive cancers appropriately processed for the demonstration of this moiety. The lipid was found in a variety of well recognized histologic types of cancer which tends to minimize the singular nature of a so-called lipid-rich variety. More importantly, moderate and marked degrees of histochemically demonstrable lipid in breast cancers were significantly associated with short-term treatment failure (6 months to 2 years).[31]

CONCLUDING REMARKS

1. The preceding represents an attempt to identify those pathologic characteristics that appear to influence the rate of treatment failure in patients with breast cancer. At this time we have no data derived from multivariate analysis which may enable us to rank the significance of the features noted as well as their independence; for example, one might ask whether the contour of the tumor border relates to prognosis independently of histologic grade. Despite this shortcoming the information concerned in this report as well as the few studies in which we have utilized multivariate analysis to a limited degree strongly suggest that the most important prognostic discriminants for breast cancer are represented by nodal status, including number of metastatic nodes, size and growth pattern of such metastases, and perhaps to a lesser degree the histologic appearance associated with uninvolved nodes; and degree of tumor differentiation which encompasses histologic type and nuclear and histologic grades. Since the nodal status can only be accurately assessed by pathologic examination, it is evident that any operation performed for cancer of the breast should be accompanied by an adequate axillary node sampling. All of this information indicates the heterogeneity of breast cancer. Such an understanding provokes the realization that its stereotyped treatment may be somewhat fatuous.

2. The pathologic problems concerning the identification of in situ and intraductal carcinomas are not within the scope of this presentation. Yet, some information has been derived from the examination of these breast specimens relative to these noninvasive forms of cancer which are pertinent to considerations concerning the efficacy of segmental mastectomy in the treatment of breast cancer. One of the principal objections to this modality has been the recognition of multicentric foci of cancers in quadrants remote from the dominant mass. In this study the incidence of such lesions was conservatively estimated to be 13 per cent with 9 per cent being noninvasive and 4 per cent invasive. Importantly, it was observed that multicentric cancers were encountered in those instances in which the dominant mass measured more than 5 cm, and the nipple and skin exhibited microscopic involvement. Thus, it would appear that pathologic examination may allow for a certain degree of confidence in predicting the presence of multicentric cancers and therefore allow for the recognition of subsets of patients that might not be suitable for segmental mastectomy. Other considerations would appear to minimize the occurrence of multicentricity as an objection to segmental mastectomy. The biologic behavior and the clinical significance of such lesions have not been demonstrated. The occurrence of two dominant primary breast cancers in the same breast is exceedingly rare, occurring in only 0.1 per cent in our studies. It has been noted that in situ or noninvasive cancers of the breast may be found in breasts of women over 70 years of age dying of other causes to be 19 times more frequent than the reported incidence of clinical breast cancer at that age.[51] Also the incidence of

multicentric cancer does not appear to be significantly greater than the incidence of bilateral breast cancer; yet, prophylactic contralateral mastectomy in the treatment of breast cancer is not a widely advocated procedure. Further, it is not clear from anecdotes whether recurrences of cancer in breasts after segmental mastectomy represent a recurrence of the dominant mass cancer or a true focus of multicentric cancer. Thus, it would appear that a carefully conducted clinical trial evaluating the effectiveness of segmental mastectomy in the primary treatment of breast cancer is not only warranted but should receive a high priority. Such a study would appear to be important not only because of its therapeutic implications but also because it should provide information relative to the biologic nature of such noninvasive lesions.

3. It is apparent that the pathologic study of breast cancer must become more meaningful than in the past for considerations relating to therapy and the biology of this disease. It is highly unlikely that the information required to satisfy these needs can be adequately provided by frozen section or rapid diagnostic techniques as now practiced. This is not intended to denigrate the value of frozen sections in the diagnosis of diseases of the breast. Yet, the time is foreseen when the utility of the frozen section will be limited. There is no evidence to indicate that the delay attendant to a complete, meaningful pathologic evaluation of breast specimens will jeopardize a satisfactory result.

ACKNOWLEDGMENT

The author gratefully acknowledges the statistical assistance provided by Dr. Carol Redmond, Project Statistician, and the many cooperating investigators who generously participated in Protocol No. 4, National Surgical Adjuvant Breast Project.

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Clinical Trials and the Surgical Treatment of Breast Cancer

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One of the major medical advances of our time has been the introduction of the prospective randomized clinical trial as a mechanism for clinical problem solving. It provides the ultimate opportunity to obtain answers to biological questions of importance which can be gotten in no other way. Despite those virtues, the vast majority of surgeons in this country have failed to become involved in or support clinical trials for a variety of unconvincing reasons, thus impairing the rapid and orderly attainment of definitive information so necessary to resolved differences that vitally concern the care of many thousands of patients. Paradoxically, however, it has been a relatively small group of surgeons in the United States and Canada who, through their participation since 1958 in protocols conducted by the National Surgical Adjuvant Breast Project (NSABP), have made and are making possible the availability of valuable data regarding the treatment of primary breast cancer.[6, 8, 10, 15] Prior to discussing protocols that relate to operative management, it is appropriate to reaffirm[3] why randomized clinical trials are so vital and to briefly put into perspective the present surgical controversy that has given rise to those trials.

The Reason for Randomized Trials

There is increasing awareness that the term "breast cancer" is an eponym employed to designate a heterogeneous group of cancers of the

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Supported by a Breast Cancer Task Force Contract (NIH-N01-CB-23876), a Grant (CA-12027) from the U.S. Public Health Service, and a Grant (RC-1313) from the American Cancer Society.

breast residing in a heterogeneous group of women. As a consequence of the multiple host-tumor permutations, consideration of the natural history of breast cancer as a single phenomenon is an anachronism.[4] The varied individual natural histories determine the results of a treatment which in turn influences the subsequent history of the disease. Not only is breast cancer a pathologically heterogeneous disease, but it evokes heterogeneous tumor and host immune responses as well. In regard to the former, findings indicate that the propensity of most breast cancers for regional and/or systemic metastases is related to quantitative and qualitative histopathologic features that reflect their growth characteristics. Relative to the latter, a multitude of host immunologic responses have been variably observed. While at present, their true significance for the natural history of the disease may be said to be obscure they cannot be dismissed as irrelevant. The finding of receptor sites in some breast cancers and not others is apt to be only one example of the heterogeneity of such tumors at the molecular level. A multitude of other differences either on the cell membrane or within the cell itself may be expected to be demonstrated. It would be naive to anticipate that such host and/or tumor dissimilarities could not be responsible for variations in tumor growth, host reaction, and response to therapy.

Thus, to talk about breast cancer as if it were a single entity is no longer justifiable, particularly when one considers the results of treatment. This reviewer has spent almost an entire professional lifetime emphasizing the need for proper controls when evaluating treatments and has pointed out that comparing results from disparate series of patients is likely to result in misleading conclusions. It is for that reason that the prospective randomized clinical trial has assumed such importance. A properly designed clinical evaluation attempts to ensure that the groups of patients being compared are similar in *all* known parameters and that unintentional bias is not likely to be a factor affecting the comparison. The ultimate aim is to attempt to ensure that the "mix" of factors which may influence prognosis is the same in the groups being compared and that the only difference between them is the treatment employed. Unfortunately, no retrospectively obtained information compared with other retrospective or even prospective observations obtained by other investigators or even the same investigator can ensure such comparability. The notion that historical controls may be employed for evaluating the results of therapy (surgical, systemic, etc.) for breast cancer is to be discredited. Even within the NSABP it has been observed that employing the same treatment arm in different protocols having similar criteria for patient eligibility, differences in results may indicate differences in the patient populations rather than in treatment itself. Consequently, to make *firm* conclusions from retrospective studies regarding the relative worth of two treatments is "an exercise in futility." In 1970 this reviewer wrote,[3] "It must be clearly and emphatically stated that it is not the intent to depreciate the retrospective studies of the past and consequently to preach therapeutic nihilism, but to put such studies in proper perspective. Just as the prime purpose of

laboratory investigation is to provide guidelines and clues as to what might be expected to occur when such studies are applied to the human, so may the results of retrospective analyses supply hints for future definitive evaluation. There is nothing wrong with good retrospective studies. The trouble is with those who have ascribed more validity to them than they deserve by failing to recognize their purpose and limitations." In summary, until surgeons are prepared to make the commitment to participate in randomized clinical trials so that answers are obtained to resolve their clinical uncertainties, they must resign themselves to the confused state of affairs which has existed for more than a decade.

Changing Rationale for Cancer Surgery

The rationale for cancer surgery is undergoing a redefinition which is in keeping with present understanding of tumor biology.[1,2] Anatomical principles of the past are being supplanted as a result of evidence indicating: breast cancer is, in most if not all cases, a disseminated disease at the time of diagnosis; removal of a primary tumor results in a variety of changes in the host and in residual tumor cells; the role of lymphatics and lymph nodes differs from that originally assigned to them; and the significance of multicentricity may not be as great as might be presumed. Such considerations are giving rise to a new biological basis for cancer surgery. If cure is dependent upon the surgical removal of absolutely every cancer cell, the outlook would indeed be bleak and operation could at best be considered a palliative procedure. The primary aim of oncologic surgery (with or without aid of radiation therapy) at present seems to be directed toward reducing the tumor burden to a number of viable cells which are entirely destroyable by host immunological (and possibly other) factors, systemically administered anticancer agents, or a combination of both.

Increasing evidence indicates that primary tumor removal may result in a variety of beneficial host changes. Moreover, its removal, by increasing the growth fraction of residual tumor cells may make them more susceptible to anticancer agents. Such findings are of profound importance and provide a rational basis for cancer surgery. Whatever proves to be the ultimate role of operation in the treatment of breast cancer, it is certain that its position will be defined by biological considerations and that the anatomic, mechanistic basis for cancer surgery is no longer entirely appropriate. The several ongoing surgical clinical trials in progress in various parts of the world should provide information that will substantiate or refute justification for a change in oncologic surgical principles.

NSABP Surgical Trials

Universal preoccupation with earlier diagnosis, the use of systemic adjuvant chemotherapy, and the search for a better biological understanding of breast cancer has, at least for the moment, tended to quiet the importance of the long existing debate regarding the proper surgical management of that cancer. This is unfortunate since, as informa-

Table 1. *Responsible Investigators and Institutions Participating in NSABP Protocol No. B-04*

INSTITUTION	RESPONSIBLE SURGEON	RESPONSIBLE RADIATION ONCOLOGIST	RESPONSIBLE PATHOLOGIST
Albert Einstein College of Medicine	Herbert Volk	Nemthalla A. Ghossein Rushby Abadir	John Molnar
Boston City Hospital	C. William Kaiser	Merrill Feldman	Leonard Berman
Creighton University	Claude H. Organ	J. R. Zastera	Wadi Bardawil
Downstate Medical Center, SUNY	Bernard Gardner	Joseph Bohorquez	Yale Rosen
Ellis Fischel State Cancer Hospital	John Spratt William Donegan	Camilo Paig	Carlos Perez-Mesa
Fitzsimmons General Hospital	Richard M. Hirata	Terry Powell	James Seab
French and Polyclinic	James McManus	Arthur Coleman	Nijole V. Brazenas
Geisinger Medical Center	C. W. Konvolinka	David Beiler	C. James Favino
Harbor General Hospital	Yosef Pilch John R. Benfield	Richard Small	Frank M. Hirose
Harrison S. Martland Hospital	Benjamin F. Rush, Jr.	John Mallams	Michael Lyons
Hennepin County General Hospital	Claude R. Hitchcock	Manoucher Azad	John I. Coe
Jewish General Hospital	Richard G. Margolese	J. J. Hazel	Claude LaChance
Louisiana State University	Isidore Cohn, Jr.	Joseph V. Schlosser	Ronald A. Welsh
Medical College of Pennsylvania	Donald Cooper	Janet Parker	Gerald Justh
Medical College of Virginia	Walter Lawrence, Jr.	E. Richard King	Saul Kay
Metropolitan Hospital	John F. Weiksnar	William Henkin	Eugene Schwartz

Michael Reese Hospital and Medical Center	Richard H. Evans	Lionel Cohen	Miriam L. Christ Wendy Recant
Montefiore Hospital and Medical Center	Richard G. Rosen	Flora Mincer	Norwin Becker
Mount Sinai School of Medicine	Gerson J. Lesnick	John Boland Harry Perlberg	Mamoru Kaneko
Oakland Naval Hospital	Vernon Fitchett	David Karp	Phillip Vogt
St. Vincent's Hospital	Thomas Nealon, Jr.	George Schwarz	William E. Delaney, III Ilona Toth
Temple University	Willis Maier	Marie LoPonte	Paul Putong
University of Arkansas	Kent Westbrook	D. R. Harris	Glenn Baker Sidney Saltzstein
University of California, San Diego (U.S. Naval Hospital)	Marshall J. Orloff James Guzik	Quintus Crews	Adelbert Cramer
University of Illinois	Tapas K. Das Gupta	Edwin J. Lieber	Jose Manaligod
University of Iowa	Richard L. Lawton	Howard B. Latourette	Frederic W. Stamler
University of Pennsylvania	Francis E. Rosato	Lawrence Davis	Horatio T. Enterline
University of Pittsburgh	Bernard Fisher	John Parsons Melvin Deutsch	Susan J. Rogers
University of Rochester	W. Bradford Patterson	Eileen Paterson	Robert A. Cooper, Jr.
University of Texas Medical Branch at Galveston	Edward B. Rowe	Marvin H. Olson	Richard Marshall
University of Texas Medical School at San Antonio	Anatolio B. Cruz, Jr.	Peter Zanca	George Bannayan
University of Vermont	Roger S. Foster	G. Stephen Brown	Roy Korson
Washington University	Harvey Butcher	Carlos A. Perez	Walter Bauer
Wayne State University	Alexander J. Walt	Alan Scheer	Barbara Rosenberg

tion accumulates relative to other aspects of the disease, the more confounded becomes the surgical dilemma and the greater becomes the need for its resolution.[9]

Until recently, the surgical controversy was quite simplistic. It was directed toward a test of the null hypothesis; i.e., that less expansive operative procedures were as good as but no better than radical mastectomy relative to survival. Operations such as modified radical, total, or segmental mastectomy have been indicated for the improvement of cosmesis rather than for the prolongation of disease-free survival. Advocates of those operations have hoped that better cosmesis could be obtained with a disease-free interval equivalent to that obtained by a more radical procedure. That total mastectomy would result in better survival than radical mastectomy or that segmental mastectomy would be better in that regard than total mastectomy has never been a serious consideration despite the suggestion that leaving axillary nodes might be advantageous.

Because of the uncertainty that affects many thousands of women with primary breast cancer each year in this country alone, in the fall of 1971, after almost a decade of planning, investigators from 34 institutions (Table 1) in the United States and Canada began participation in a National Surgical Adjuvant Breast Project (NSABP) protocol (B-04), comparing alternative treatments of primary operable breast cancer with radical mastectomy. The specific aims of the study were to determine, in patients without clinical axillary node involvements, if total (simple) mastectomy is as effective as radical mastectomy, provided that patients having total mastectomy who subsequently develop significant palpable nodes have them removed, and whether total mastectomy with postoperative regional radiation is as effective as radical mastectomy or total mastectomy with postponement of axillary dissection until significant palpable nodes occur. In patients having clinical axillary node involvement, the primary aim was to ascertain

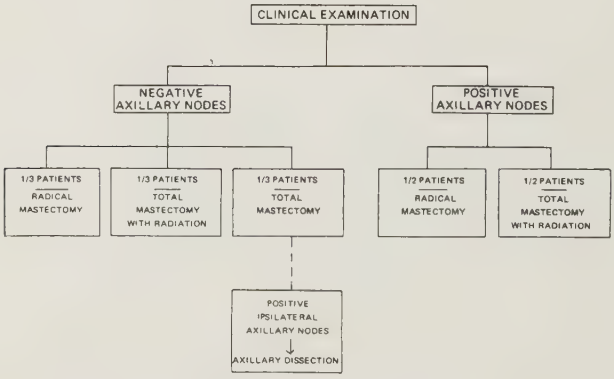

Figure 1. National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP) Protocol No. B-04 – Schema.

whether radical mastectomy and total mastectomy with regional radiation are equivalent procedures. In addition to supplying information relative to the merits of the various treatments, it was hoped that this investigation would provide data of biological significance, particularly that which would confirm or repudiate the worth of en bloc dissection in cancer surgery.

This protocol does not compare total mastectomy alone with radical mastectomy, as has been improperly reported in both the lay and medical press. Consequently, any reference to total mastectomy implies that patients having total mastectomy alone, who subsequently develop significant palpable lymph nodes, have the nodes treated by axillary dissection, and that the finding of such nodes do not represent a treatment failure unless they cannot be removed. The occurrence of such nodes in patients receiving total mastectomy and radiation does represent a treatment failure.

All patients with clinically curable breast cancer meeting specific protocol requirements were eligible. The first patient was admitted to the trial in August, 1971. Women were randomized (Fig. 1) into three therapy groups: radical mastectomy, total mastectomy, and total mastectomy with regional irradiation. Those patients with clinically positive axillary nodes were randomly assigned to radical mastectomy or total mastectomy with regional irradiation. Radiation therapy was begun six weeks following mastectomy. In general, the plan was to deliver a dose of 5000 rad to the chest wall, 4500 rad to the internal mammary nodes, 5000 rad to the mid-plane of the axilla, and 4500 rad to the supraclavicular area in five weeks. In August, 1974, when almost 1700 patients had been entered, patient accession was discontinued. Information concerning patient selection, plan of investigation, patient entry, patient and tumor characteristics, operative procedures, radiation therapy, end-points and follow-up of the study has been presented in detail.[5] The trial is now in its seventh year. Results published at a time when patients were on study for an average of 36 months failed to demonstrate an advantage for those who had a radical mastectomy.

No significant difference in the treatment failure or survival was observed between patients with clinically negative nodes who had a conventional radical mastectomy and those managed by total mastectomy with postoperative regional radiation; nor was there a significant difference between patients having a radical mastectomy and those having a total mastectomy and an axillary dissection only if positive axillary nodes subsequently occurred. Similarly, no significant difference in treatment failure or survival existed between patients with clinically positive nodes who were treated by radical mastectomy or by total mastectomy followed by radiation. Updates of the data have been made and presented to the NSABP membership after the mean time on study for all patients was four and five years.[11, 14] The findings have remained similar to those obtained at three years. Since the data have not yet been officially published, they cannot be presented in this overview.

In that study it was observed that 40 per cent of patients with clinically negative nodes having a radical mastectomy were found to have histologically positive nodes. Consequently, approximately 40 per cent of patients having total mastectomy alone should have had tumor positive axillary nodes left unremoved. Of particular interest has been persistent observation that to this time (mean 5 years on study) only 15 per cent of patients undergoing total mastectomy have developed positive nodes requiring an axillary dissection. The persistence of such a difference between the anticipated incidence and actual occurrence of nodal involvement would have profound biological significance. Such a finding might suggest that some nodes containing tumor may never assume clinical significance. Moreover, it may be conjectured as to whether in some there is tumor regression. The finding that leaving behind positive axillary nodes has not increased the incidence of distant metastases or the overall proportion of treatment failures, and that a disproportionate number of treatment failures in the total mastectomy group occurred in those patients who subsequently required axillary dissection, reinforces the view that positive axillary lymph nodes are not the predecessor of distant tumor spread, but are a manifestation of disseminated disease.

As a result of emphasis on early diagnosis, the use of systemic adjuvant therapy and a new understanding of the disease, the decision relative to choice of operation may seem to have become more rather than less complicated. A new set of complex questions requiring immediate answers have been engendered. Do patients with "minimal" cancers really need to have total removal of a breast? Does the multicentricity of breast cancer preclude employment of a segmental mastectomy? What is the clinical significance of such occult lesions? Is it now likely that breast irradiation and/or systemic chemotherapy will ensure the probability that lesser operative procedures will be equivalent to those that are more extensive?

Because of evidence from several retrospective studies, one prospective study, findings from the aforementioned NSABP clinical trial, and observations utilizing adjuvant chemotherapy, there is ample reason to anticipate that segmental mastectomy might have a place in the management of certain patients with primary breast cancer. Convinced that there is more ethical and scientific justification for carrying out a clinical trial to confirm or repudiate that contention than for not doing so, the NSABP has recently implemented such an evaluation (Protocol No. B-06). Since segmental mastectomy or some version of it ("lumpectomy," quadrantectomy, etc.) is for the most part being carried out in an uncontrolled fashion throughout the world and no firm information is apt to be derived from those solo efforts, there is no question that such a trial should be undertaken; the only question is "how."

One of the major deterrents to the acceptability of such a limited resection is the realization that is may leave behind clinically and pathologically undetected de novo cancers at sites within the breast remote from the dominant mass. That breast cancer is a multicentric

phenomenon is beyond question.[10, 11] Similarly, there is evidence to indicate that the incidence of cancer in the contralateral breast may be much greater than previously supposed. The disturbing fact is that despite the significant incidence of multifocal lesions in both breasts of a woman with a primary breast cancer, only rarely will there be evidence of two or more clinically overt primary cancers in the same breast. Similarly, the presence of synchronous bilateral tumors is uncommon and the incidence of a second asynchronous primary tumor in the involved breast fails to approach the incidence of occult lesions detected by random biopsy or autopsy. For example, it has been noted that incidence of clinically latent intraductal carcinomas in breasts of women over the age of 70 who died from causes other than mammary carcinoma to be 19 times greater than the reported incidence of clinical breast cancer. Such findings are highly suggestive that all cancers do not progress to overt lesions or may even undergo regression. That such a possibility is not remote comes from the knowledge that neuroblastomas of the adrenal glands in children, thyroid carcinomas, and carcinomas of the prostate are found more frequently in random pathologic material examined than they are found clinically in comparable populations.

It is of the utmost urgency that the clinical significance of occult multicentric cancers be ascertained in order to define correct surgical strategies. At present, it is difficult for surgeons resorting to orthodox principles of cancer management to accept the possibility that "a cancer may not be a clinical cancer!" From a basic biological point of view, there seems to be a need for information relating the kinetics of growth of such tumor foci to those of the primary tumor. Does the

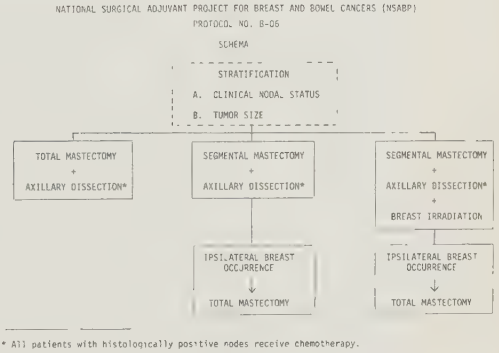

Figure 2. National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP) Protocol No. B-06—Schema.

Table 2. *Responsible Investigators and Institutions Participating in NSABP Protocol No. B-06*

INSTITUTION	RESPONSIBLE SURGEON	RESPONSIBLE RADIATION ONCOLOGIST	RESPONSIBLE PATHOLOGIST
Boston University	Peter Deckers	Merrill I. Feldman	Philip Gordon
Hotel-Dieu (Quebec)	Louis Dionne	Jacques Laverdiere	Real Legace
Jewish General	Richard Margolese	Julio Guerra	Claude LaChance
Kaiser Permanente (Portland, OR)	Peter Feldman	John Molendyk	George Chan
Memorial Cancer Research Foundation	Gerald Glantz	Irwin Grossman	Victor Rosen
Metropolitan Hospital	John Weiksnar	William Henkin	Eugene Schwartz
Montreal General	John MacFarlane	Julio Guerra	W. P. Duguid
Pennsylvania Hospital	Harvey Lerner	John Glassburn	Else Olen
Royal Victoria	Henry Shibata	Julio Guerra	Giles Tremblay
St. Luc Hospital	Roger Poisson	Jean Philip Mercier	Jean Cote
St. Michael's	Leo Mahoney	Roy Clark	Ara Chalvardjian
University of Calgary	Peter Cruse	Keith Arthur	Fred Alexander
University of California (San Diego)	Yosef Pilch	Joella F. Utley	Sidney Saltzstein
University of Maryland	E. George Elias	Ill Soo Kim	Cyril Toker
University of Pittsburgh	Bernard Fisher	Melvin Deutsch	Edwin R. Fisher
University of Vermont	Roger Foster	James Gagnon	Roy Korson
Washington University	Marc Wallack	Carlos Perez	Walter Bauer
Wilmington Medical Center	Leslie Whitney	Donald Tilton	Patrick Ashley

presence or absence of a primary tumor influence their growth? Are their kinetics similar to those of distant metastatic foci? Will they become more susceptible to destruction by antitumor agents following removal of the primary? Is radiation an effective agent to eliminate them?

The NSABP study began in June of 1976 and includes participants and institutions from the United States and Canada (Table 2). Its aim is to determine whether cosmetically acceptable preservation of the breast in a subset of patients with primary cancer can be achieved without unfavorably influencing treatment failure and survival rates as well as morbidity. Moreover, the study should provide evidence to indicate the clinical significance of microscopic multifocal tumor in the breast.

Appropriate patients who are eligible for segmental mastectomy as defined by the protocol following stratification according to nodal status and tumor size are being randomized equally into one of three groups (Fig. 2). They are treated either by total mastectomy and axillary dissection, segmental mastectomy and axillary dissection, or segmental mastectomy and axillary dissection followed by radiation to the breast. Patients in all three groups found to have histologically positive axillary nodes receive adjuvant chemotherapy. Patients in the two segmental mastectomy groups who subsequently develop a tumor in the ipsilateral breast are subjected to total mastectomy. When radiation therapy is employed, it is given to the entire breast at doses between 5000 and 5500 rads over five weeks according to meticulous protocol requirements.

This trial could provide the most significant information to be made available in the last 100 years regarding the operative management breast cancer. Aside from the biological importance of the findings, should it be demonstrated that segmental mastectomy could supplant total removal of the breast, there would be provided to women a viable and meaningful incentive for the earlier identification of breast cancers. Such an event would not only produce a positive gain in terms of cosmesis, but would also provide the proper setting for greater curability. For, it is likely that under such circumstances, systemic therapy will be most effective.

Despite the unquestionable importance of such a clinical trial for the countless women who will develop breast cancer, it will succeed only if surgeons and their patients are willing to participate. There is no other way to obtain the data needed to determine with assurance whether women (at least some) can be spared the mutilation of mastectomy. To date, there are approximately 200 patients who are participants in this protocol. This author appeals to those breast cancer surgeons who recognize the urgency of this problem and who are willing to participate in this protocol to contact the NSABP.

Comment

Findings to date from NSABP Protocol B-04 engender comments which are provisional and depend upon further patient follow-up. It is

reasonable to expect that after five years, the mean time that patients have been on that study, major trends have been firmly established. When all information is considered, there would seem to be little justification for continuing to believe that the conventional Halstedian radical mastectomy is superior to all other operations for local-regional disease control that its use results in a lower incidence of distant metastases with greater patient survival.

With employment of systemic adjuvant chemotherapy in patients at great risk for recurrence, i.e., those with positive axillary nodes, it has become necessary that axillary nodal "staging" be carried out no matter what the operation relative to the breast. Consequently, total or partial mastectomy without axillary intervention has no clinical merit. Moreover, although only 15 per cent of patients having a total mastectomy required a delayed axillary dissection, that proportion could have been spared a second operation by primary removal of lymph nodes — a procedure adding little to the cosmetic deficit resulting from total mastectomy alone. Thus, to reiterate, it is our conclusion that at this time no matter what operation is employed axillary intervention is indicated.

The results of the total versus radical mastectomy protocol provide indirect evidence to substantiate the worth of "modified radical," or more appropriately "modified total," mastectomy relative to that of radical mastectomy without the need for a direct comparison (prospective clinical trial) of the two. The reader may not appreciate the fact that despite its common usage there has never been a direct comparison, i.e., clinical trial, to determine whether modified radical mastectomy is or is not equivalent to radical mastectomy.

Segmental mastectomy for the treatment of breast cancer is justifiable only within the confines of a proper clinical trial such as is being carried out by NSABP (Protocol B-06).

While to our knowledge the two NSABP studies represent the only prospective randomized clinical trials in this country and Canada specifically directed toward evaluating the worth of various surgical procedures for breast cancer, it would be remiss not to call attention briefly to several of the more prominent trials of surgery which have been and are being carried out abroad. Since 1969 Hayward and associates at Guy's Hospital, London, England, have been evaluating wide local excision of breast cancers. Between 1961 and 1971, 370 patients with clinical Stages I and II cancers aged 50 years or over were randomized so as to receive either wide local excision or standard radical mastectomy. Both groups of patients received postoperative radiation which, by the investigator's own admission, would not be considered optimal according to today's standards for treating an intact axilla. While wide excision was followed by a higher incidence of local recurrences (predominantly in the unremoved axillary nodes) there was no significant difference between the two treatment groups in 5 and 10 year survival.[12] From 1971 on only those patients in whom the axilla was thought to be negative ($T_{1,\ 2}$, $N_{0,1a}$, M_0) were considered to be eligible, and patients under 50 years were included. This second half of the trial con-

tinued until January, 1975, and an additional 276 patients were entered. No data are yet available relative to the latter.

Another trial of conservative treatment of breast cancer is that by Veronesi at the National Cancer Institutes in Milan, Italy.[16] In 1973 he began a clinical trial in which patients with Stage I (T_1, N_0, M_0) breast cancers $\leq$ 2 cm in diameter received either a partial mastectomy plus axillary dissection plus postoperative radiation (6000 rads) to the involved breast or conventional radical mastectomy. Patients with positive lymph nodes in the partial mastectomy group were further randomized to receive either additional radiotherapy to the supraclavicular and internal mammary node areas or no additional radiotherapy. By June, 1976, 302 patients were entered into that trial. In January, 1976, the protocol was changed so that all node positive patients receive adjuvant chemotherapy with cyclophosphamide, methotrexate, and 5-Fluorouracil for one year. In his report of 1977, the investigator noted no significant differences between the treatment groups.[16]

Another trial of conservative surgery is that of the Cancer Research Campaign of Great Britain under the leadership of Murray.[13] Between 1970 and 1975, 2268 patients with clinical Stages I and II breast cancers ($T_{1,2}$, $N_{0,1}$ M_0) were randomized between simple mastectomy plus postoperative radiotherapy or simple mastectomy followed by a watch policy with further treatment employed only for recurrent disease. After five years of follow-up, there was no evidence that postoperative radiotherapy increased survival or decreased the incidence of distant metastases, although it was advantageous as in the NSABP protocols in preventing local recurrence.

Conclusion

It would seem that as a consequence of clinical trials that have been and are being carried out, the breast cancer surgical dilemma is "sorting out." At present, data would seem to indicate that for clinical Stages I and II cancers ($T_{1,2}N_{0,1a,b}$, M_0), modified total mastectomy, i.e., total removal of the breast and axillary "dissection," has supplanted radical mastectomy as the "standard" therapy. The next challenge is to determine specifically which patients will fare as well with segmental mastectomy as with the present "standard" operation and to define how best to coordinate surgical efforts with those of other members of the "family" of modalities which are now, or will be, available for the treatment of primary breast cancer.

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Partial Mastectomy

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Partial mastectomy, sector mastectomy, segmental mastectomy, and extended tylectomy (gr. Tylos=lump) define an operation that locally excises a breast cancer and surrounding parenchyma. It is used as a curative operation for breast cancer with or without axillary dissection.

Despite some favorable reports about this operation, there is considerable controversy based on emotion, theory, and limited patient follow-up.[2-4] The long-term results, and the effects on survival of new or recurrent tumors in the ipsilateral breast, and of development of subsequent axillary metastases in undissected axillas have not yet been determined. This article traces the development of partial mastectomy, outlines its present role, and presents preliminary results in 160 patients followed 5 to 21 years after partial mastectomy at the Cleveland Clinic.

HISTORY

Local excision of breast tumors has been practiced since the beginning of the surgical treatment of breast cancer, but until recently its success and application were limited because of the size and bulk of the tumors. As breast cancers have become smaller and axillary metastases fewer, renewed interest in partial mastectomy has developed.

Initially, the operation was used in older patients with coexisting serious systemic diseases or as a palliative operation. Adair reviewed 1419 breast cancer patients.[1] Sixty-three were treated by local excision. "If one were to judge the results of all the cases by the accomplishments of treatment of 97 simple mastectomies and the 63 local removals," Adair said, "it would appear that such local procedures would be preferable." Then he goes on to try to explain away the good results.

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Based on these data (and perhaps challenge), several studies followed. In 1964, Porritt summarized a 12 year experience comparing "segmental mastectomy" plus x-ray therapy (when axillary nodes were involved) with standard radical mastectomy.[4] Of 263 treated patients, 65 per cent survived five years after segmental mastectomy compared with 50 per cent after radical mastectomy. At 10 years 45 per cent of those treated by local operations were living, as were 34 per cent of those treated by radical mastectomy. The differences were not statistically significant, but less morbidity and deformity followed segmental mastectomy.

In England sector mastectomy plus postoperative irradiation of the breast and axilla was performed in 77 patients between 1953 and 1965 by Hermon Taylor and associates.[7] Fifty-six patients survived five years (71 per cent) and 32 for 10 years (50 per cent). Thirty-seven per cent had involved axillary nodes, and the mean tumor size was 3.3 cm. Seventy-four were scirrhous carcinomas.

Criticisms of nonrandomized studies apply to the above studies. Case selection, special characteristics of the tumor, small numbers of patients, varying follow-up periods, and few follow-ups longer than 10 years limit the value of these studies. Many included doses of radiation therapy varying from adequate to 30 per cent under effective levels.[2, 3, 5] Nevertheless, all studies point to the fact that in properly selected cases, partial mastectomy or local excision plus radiotherapy are effective in treating small breast cancers. In comparable cases, the end results are similar to those following mastectomy.[3]

THE GUY'S HOSPITAL STUDY

Atkins et al. attempted to avoid criticisms of the earlier studies by randomizing 370 women age 50 and over to undergo partial mastectomy or radical mastectomy with and without radiotherapy.[2] One hundred eighty-eight women had radical mastectomy, postoperative radiotherapy (2500 to 2700 rads) to the axilla, supraclavicular triangle, and internal mammary nodes, and prior to 1969 three doses of Thiotepa. The remaining 182 patients had extended tylectomy plus postoperative radiotherapy to the axilla and supraclavicular triangle (2500 to 2700 rads plus 3500 to 3800 rads in three weeks to the breast). Prior to 1969, three doses of Thiotepa also were given. Life table analysis for periods up to 10 years revealed no significant differences in the survival of those without clinical evidence of axillary involvement (clinical Stage I) whether treated by radical or partial mastectomy. In patients with axillary metastases (Stage II), the 10 year survival was significantly better and fewer distant metastases were present after radical mastectomy. However, at the time of this report, the number of patients with clinical Stage II cancer who had been treated 10 years before was too small to be of statistical significance. Since the time of the report, the differences in results have tended to diminish strikingly.

While the prospective design of this study should avoid the criticism of several others, it has been criticized because of inadequate treatment of involved axillary nodes by the low dose of radiotherapy used or by leaving clinically suspicious axillary nodes at the time of surgery.

CLEVELAND CLINIC STUDIES

In the United States, Crile has been the spokesman for partial mastectomy. Beginning in 1955, he organized several studies both to evaluate partial mastectomy and to compare it with mastectomy operations. Subsequently, between 1955 and 1964, 57 patients treated by local excision of breast tumors were reviewed. This constituted less than 11 per cent of breast cancer operations at the Cleveland Clinic. The patients were carefully selected on the basis of: (1) small peripheral lesions; (2) advanced age; (3) severe intercurrent disease; or (4) for palliation in combination with radiation in patients with small primary tumors and advanced local disease. Additional treatment for patients with clinical Stage I disease included axillary dissection in six and cobalt therapy in three. Sixty-seven per cent of patients survived five years (34 were tumor free and three had metastases). This survival rate was similar to patients treated by mastectomy. After partial mastectomy, 72.5 per cent with Stage I lesions and 53 per cent with Stage II lesions survived five years.[3] After mastectomy, 745 of patients with Stage I lesions and 54 per cent of patients with Stage II lesions survived five years. There was no difference in local recurrence (5 per cent in each group). A first appearance of cancer in an axilla that had not been dissected or irradiated is not considered to be a local recurrence.

In 1975, patients who had undergone partial mastectomy and had been followed for 10 to 15 years were compared with those who had modified radical mastectomy in terms of invasion, cancer size, and involvement of nodes. As summarized in Table 1, survival and local recurrence were similar after both operations. The limitations of this study are obvious—small numbers of patients, nonrandomized selection, and a relatively short follow-up.

Table 1. *Results of Partial Mastectomy in 162 Patients at the Cleveland Clinic from 1957 to 1972*

YEARS	ALIVE	DEAD	INCOMPLETE FOLLOW-UP
1 to 5 years	10	37	4
5 to 10 years	64	20	11
10 to 15 years	15	4	4
>15 years	9	1	7
TOTAL	98	62	26

PRELIMINARY REPORT OF LONG-TERM RESULTS

In the hopes of correcting the limitations of our previous studies, we retrospectively reviewed the results of 160 partial mastectomies done for breast cancer. The patients were followed from 5 to 21 years until 1977. This report is preliminary because 26 patients were not followed to this time (Table 1). It is published despite the incomplete follow-up in these patients, as there is enough evidence to lend further support to the rationale and validity of partial mastectomy in selected cases as a primary operation for breast cancer. Most of the operations, particularly in the earlier years, were performed by George Crile, Jr., whose assistance is acknowledged and appreciated.

Material

Between 1957 and 1972, 162 women underwent partial mastectomy for breast cancer at the Cleveland Clinic. Two have been excluded because the diagnosis was cystosarcoma phylloides. Selection of patients was not randomized. In the early years of the study the operation was done in elderly patients with serious coexisting medical conditions and limited life expectancy, whereas in the later years smaller peripheral tumors in younger patients were selected for partial mastectomy. Infiltrating ductal carcinoma was the most common lesion in 90 per cent of patients.

Results

The results to date are summarized in Table 1. Ninety-eight patients are alive and 62 have died. Of the 98 survivors, only six have been followed less than five years. Seventy-five per cent have survived five years and 45 per cent have survived 10 years.

Deaths

Thirty-seven of 62 deaths occurred within five years, and 20 occurred between 5 and 10 years. Nearly half of the deaths were due to cancer. The remaining deaths were usually due to cardiac disease.

Length of Follow-up

The crucial figure in follow-up is the fate of 26 patients not followed to 1977. However, 11 of these patients have been followed for more than 15 years, and 11 others were followed 5 to 10 years. Only 4 of the 26 have been followed less than five years and are excluded from this analysis. Of all survivors, 67 have been followed 10 years, 25 for 10 to 21 years, and eight for 1 to 5 years.

Recurrences Without Axillary Dissection

A unique opportunity to evaluate axillary metastases exists in this study, as 115 of 160 women did not have axillary dissection as part of the initial operation. Lymph node metastases developed in eight patients (7.9 per cent). The delayed treatment of axillary nodes did not alter the prognosis, as treatment with cobalt or axillary dissection was then done. Five of the eight are living without disease (Table 2). When cancer developed in the remaining breast (8 patients), mastectomy

Table 2. *Results of Partial Mastectomy in 115 Patients Without Axillary Dissection at the Cleveland Clinic from 1957 to 1972*

YEARS	ALIVE	DEAD
1 to 5 years	6	30
5 to 10 years	46	11
10 to 15 years	10	3
>15 years	7	1
TOTAL	70	45

was satisfactory treatment in four. Twenty-six other patients developed axillary metastases at the time of systemic metastases (bone, lung, or liver).

Discussion

The data in this study show that partial mastectomy with or without axillary dissection is followed by a relatively good life expectancy. Theoretical arguments against partial mastectomy have included "a violation of cancer surgical principles" and "an inadequate cancer operation." In addition to these arguments, recent pathological studies have shown that "simulated partial mastectomy" in radical or modified radical mastectomy specimens would leave foci of intraductal or infiltrating cancer in 20 to 30 per cent of cases.[6] This histologic finding reported by Rosen et al. does not seem to correlate with our clinical follow-up in which only eight patients developed a recurrent or new primary lesion, one of whom had a new primary cancer (different cell type) at 15 years.

Final follow-up will not be complete until all patients have died of natural causes or disease. The present data indicate that in selected cases the results of partial mastectomy are equal to those of other radical operations done for patients with the same stage of the disease. The 5 and 10 year survival are similar to modified radical mastectomy reported in many institutions and studies.

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Modified Radical Mastectomy

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Operative resection is most effective in the treatment of breast cancer when the cancer is limited to a localized anatomic area. To ensure complete removal, the tumor and an adequate margin of surrounding breast tissue must be removed. In addition, the removal of regional (axillary) lymph nodes has been advocated because of the high incidence of metastases to the axillary node group. The major areas of controversy regarding the surgical management of breast cancer are (1) what constitutes an adequate anatomic local excision and (2) does removal of the regional (axillary) lymph nodes provide curative benefit or does it provide only prognostic information?

Modified radical mastectomy appeals to many surgeons because it is an effective operation for breast cancer, provides staging information through removal of axillary lymph nodes, and is cosmetically acceptable. Breast reconstruction can be performed at a later time if the patient desires it.

HISTORICAL REVIEW

Prior to the development of the radical mastectomy by Halstead in 1894,[7] the results of breast surgery for cancer were dismal, with operative mortality ranging from 1.7 to 23 per cent and 3 year survival rate from 4.7 to 30 per cent.[15] The contribution of Halsted was important in that he reported an operation with an increased survival rate and lower operative mortality.[7, 8] The radical mastectomy was designed to remove widely the large breast cancers commonly seen in the late 1800's by removing the entire breast, pectoralis major and minor muscles, and axillary contents en bloc. In 1907 Halsted[8] reported a survival rate of 32.3 per cent at 3 years and 29.8 per cent at 5 years in 232 patients with an operative mortality of only 2.5 per cent, a rate considered low for that time.

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In 1906, Handley[9] described an operation similar to Halsted's except that it preserved the pectoralis major muscle; he felt it was suited for most cases of breast cancer not involving this muscle. Patey and Duson[19] in 1938 modified this operative procedure and described the basic tenets of the modified radical mastectomy. A transverse incision was used, skin flaps were cut thick, and skin grafting was rarely required. The pectoralis minor muscle was removed, but the pectoralis major was preserved. This approach was later modified by Madden[14] and by others;[15] the breast and axillary contents were removed in continuity, but the pectoralis major and minor muscles were preserved.

One of the questions raised by this operative procedure has been whether adequate clearing of the axillary lymph nodes could be accomplished without removing the pectoralis major and minor muscles. Nemoto and Dao[17] studied this issue and found that there was no difference in the number of nodes removed when 121 consecutive radical mastectomy specimens were compared with 111 consecutive modified radical mastectomy specimens.

Theoretical Advantages of Modified Radical Mastectomy

The morbidity associated with radical mastectomy can be significant. In a series of 1323 patients reported by Say and Donegan,[21] 36 per cent had significant skin flap necrosis and 31 per cent had lymphedema of the arm after radical mastectomy. In addition, the loss of skin grafts occurred in 32.8 per cent of the patients. The disfigurement associated with radical mastectomy can be considerable (Fig. 1) with the loss of contour of the chest wall. The operation has been feared by many women with breast cancer. The modified radical mastectomy removes the same anatomic areas as does the radical mastectomy in a more cosmetic fashion, preserving the chest wall muscles. When a horizontal incision and healthy skin flaps are used, it results in a cosmetically superior scar that allows for the wearing of low-cut dresses without noticeable disfigurement (Fig. 2). In addition, breast reconstruction can be performed at a later time with excellent cosmetic results. Arm swelling and disability are minimized and recuperation is

Figure 1. Patient after left radical mastectomy with a longitudinal incision who received postoperative radiation.

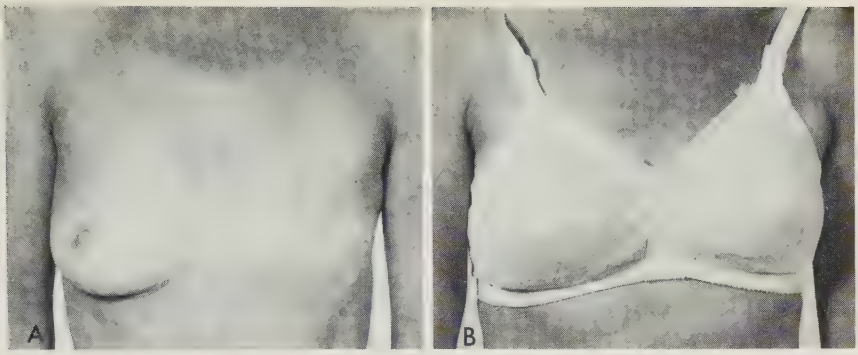

Figure 2. *A*, Patient after left modified radical mastectomy with a transverse incision. *B*, Same patient wearing a brassiere and a breast prosthesis.

rapid after a modified radical mastectomy. All this appears to be accomplished with no difference in survival and no increased incidence of local recurrence as compared to the radical mastectomy.

TECHNIQUE OF OPERATION

Biopsy

The need for biopsy of a breast mass should always be discussed with the patient and her husband, if present. The recommendation of operative biopsy by a surgeon may cause a variety of emotions depending on the patient's preconceived knowledge of the significance of breast masses, the possibility of having breast cancer, her previous exposure to other women who have had a mastectomy, the importance she places on her breast as part of her "body image," her self-esteem, and the stability of her marriage. Most women accept the recommendation for biopsy quietly with sensible and realistic questions, some stoically, others with tears, some with irrational panic.

In most patients, we perform needle aspiration of a breast mass, whether cystic or solid, initially in the office and obtain cytologic interpretation of any cells in the fluid. If the mass is a cyst and disappears, biopsy is not necessary. If the mass is solid, needle aspiration cytology frequently provides important preoperative information: "no tumor cells identified" or "atypical cells compatible with malignancy." With the later report, operative biopsy of the breast mass is essential. Because of occasional false-positive cytology reports with benign intracystic papillomas or with cellular fibroadenomas, cytologic study of a breast mass alone is not as yet acceptable for the diagnosis of carcinoma.

Operative biopsy of a breast mass may be performed with the patient awake or asleep; choice of anesthetic should be the patient's preference. Frozen section reports are obtained. If the patient is awake and the diagnosis is carcinoma, mastectomy may be performed immediately if the patient has been prepared and wants to go ahead immediate-

ly, or the operation may be delayed for up to two weeks. If the patient is asleep and the diagnosis is carcinoma, we recommend immediate mastectomy. However, some patients want only biopsy under the initial general anesthetic, and prefer to awaken and discuss further treatment after frozen section report has been confirmed by permanent section study. Delay of up to two weeks is safe. The choice of anesthetic should not be the major issue it has developed into during past years.

Modified Radical Mastectomy

We prefer and emphasize the cosmetic advantage of transverse incisions in performing a mastectomy (Figs. 3 and 4*A*). The scar is kept below the axilla (lower border of the axillary hairline) and lies within the area covered by a brassiere. We elevate first the upper, than the lower skin flaps, leaving healthy, thick skin flaps nourished by good blood flow. There is no evidence that thin skin flaps prevent recurrence; in fact, they may promote it since circulating tumor cells apparently gravitate to areas of tissue injury or hypoxia. With healthy chest wall skin, breast reconstruction is possible. The skin flaps are raised superiorly to encompass all breast tissue (Fig. 4*B*), medially to the sternum, inferiorly to the rectus sheath (Fig. 4*C*), and laterally to the latissimus dorsi muscle. The breast tissue and underlying pectoral fascia are then dissected from the pectoralis major muscle; dissection is carried between the pectoralis major and minor to remove the fat pad and group of nodes (Rotter's nodes) between the pectoralis major and minor; and then is carried laterally, removing the fascia over the pectoralis minor muscle, leaving the muscle intact. At the lateral edge of the pectoralis minor muscle, dissection is carried down through the clavipectoral fascia which invests the axilla, entering the axilla at this point.

The axilla is then opened widely by incising clavipectoral fascia superiorly over the axillary vein, exposing the vein. Dissection of the axilla is begun while an assistant elevates the pectoralis minor muscle, removing all axillary lumph nodes and fatty tissue from below the axillary vein, preserving only the nerve and blood supply to the pec-

Figure 3. Transverse incision is kept below the axillary hairline.

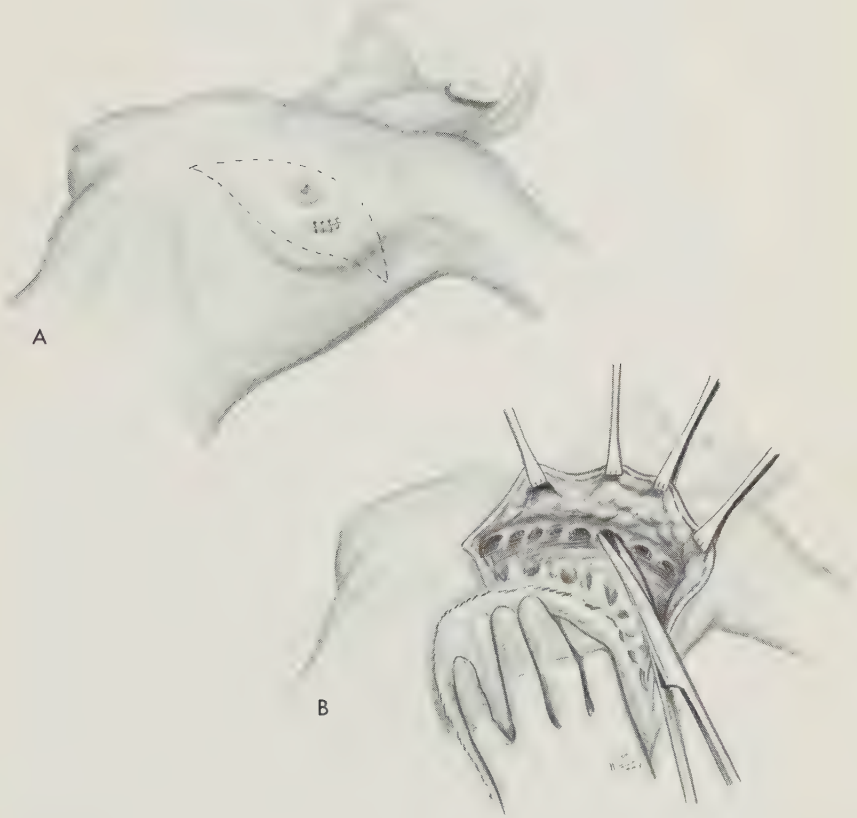

Figure 4. *A*, Outline of transverse incision is marked on the skin of the breast with sterile marking solution prior to making the incision. *B*, Upper skin flap is dissected from breast tissue.

Figure continued on following pages.

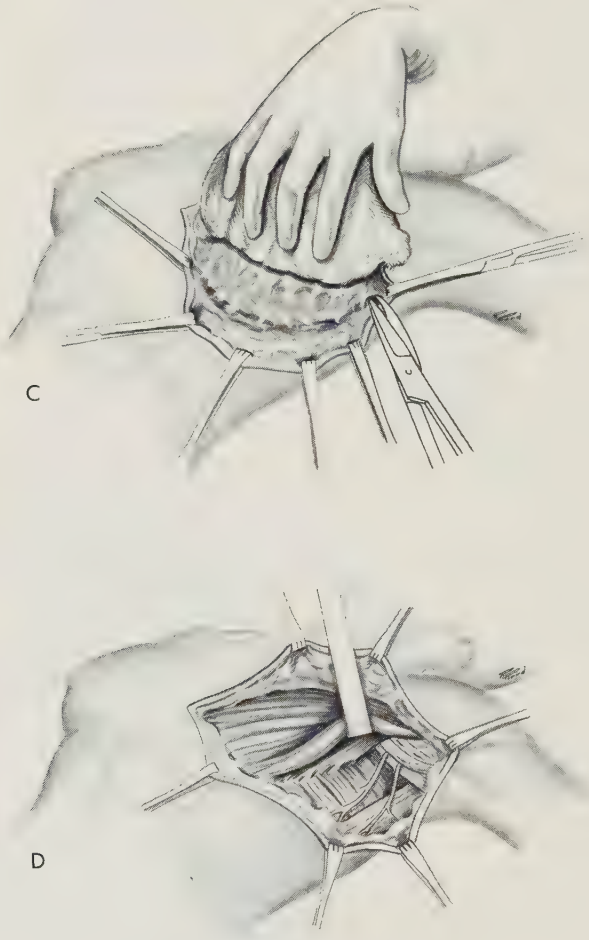

Figure 4 *Continued.* *C*, Lower skin flap is dissected from breast tissue. *D*, Completed modified radical mastectomy field. Pectoralis major muscle is retracted to show the pectoralis minor. Long thoracic nerve and thoracodorsal nerve are depicted.

Figure 4 *Continued.* *E*, Incision has been closed and suction catheters placed for postoperative drainage. A light dressing will be applied.

toralis major and minor muscles at the apex of the axilla, the long thoracic nerve along the lateral chest wall, and the thoracodorsal nerve to the latissimus dorsi, found further laterally (Fig. 4*D*). The specimen is removed and the wound area is irrigated with sterile water (not saline) to remove any bits of fat or devitalized tissue. Sterile Hemovac catheters are introduced through the lower skin flap for postoperative suction and the incision is closed with interrupted subcutaneous, absorbable sutures and interrupted skin sutures (Fig. 4*E*).

The conservative radical mastectomy, as described by Patey and Duson in 1938 and continued by Handley and by others, differs from this operation in that the pectoralis minor muscle is removed with the breast specimen, preserving only the pectoralis major muscle. If the pectoralis minor is removed, great care must be taken to preserve the nerve and blood supply to the pectoralis major as the pectoralis minor is dissected and its insertion into the coracoid process is divided. In addition, Handley has stated that, "about half the patients require a skin graft to close the wound."[10] We almost never find it necessary to use a skin graft after a modified radical mastectomy.

RESULTS

During the past 21 years at the Cleveland Clinic we have performed a modified radical mastectomy or a complete mastectomy with limited axillary dissection in approximately 70 to 75 per cent of all patients with breast cancer. From 1957 to 1972, a period in which we

Table 1. *Operations for Stages I and II Breast Cancer at the Cleveland Clinic from 1957 to 1970*

OPERATION	NO. OF PATIENTS	PER CENT OF PATIENTS
Radical mastectomy	4	0.5
Modified radical	347	49
Complete mastectomy without axillary dissection	271	38
Partial mastectomy	88	12
TOTAL	710	99.5

believed that axillary dissection and removal of "uninvolved" lymph nodes served no useful purpose and could in fact be harmful in that it interfered with regional lymph node immunity, a principal host mechanism of defense, and increased the incidence of postoperative lymphedema of the arm, we performed modified radical mastectomy in 49 per cent of women with clinical Stages I and II (potentially curable) breast cancer. During these years, complete mastectomy without axillary dissection (simple mastectomy) was performed in 38 per cent of patients, and partial mastectomy in approximately 12 per cent of patients (Table 1).

In about 1972, we began to change our thinking in regard to axillary dissection. From follow-up study of our own patients, we observed that axillary dissection did not change long-term survival in those patients whose lymph nodes were negative as compared with other patients with clinically negative nodes who did not have axillary dissection. Second, axillary dissection had an important value in that it provided more accurate staging information for patients with breast cancer. We, as well as others, began to consider the need for systemic therapy for those patients who had evidence of spread of breast cancer by virtue of metastases to axillary lymph nodes. Finally, the overall increase in late lymphedema of the arm which occurs after axillary dissection in modified radical mastectomy (2 to 3 per cent) did not seem significant enough to outweigh the advantage of more accurate staging.

Since about 1972, therefore, we have changed our philosophy and now perform modified radical mastectomy or complete mastectomy with limited axillary dissection in approximately 80 per cent of pa-

Table 2. *Percentages of Five and Ten Year Survival in Patients with Breast Cancer at the Cleveland Clinic from 1957 to 1970*

	5 YEARS	10 YEARS
All patients, all stages	59	37
Clinical stages I and II	71	46
Clinical stages III and IV	9	3

Table 3. *Percentages of Five and Ten Year Survival in Patients with Stages I and II Breast Cancer Treated by Radical Mastectomy*

	5 YEARS	10 YEARS
NSABP 23 institutions 826 patients 1958 to 1963	64	46
NCI Cancer Registry 14,000 patients 1955 to 1964	61	43

tients with clinical Stages I and II breast cancer. At the same time, our favorable experience with partial mastectomy has encouraged us to increase the application of this operative procedure to about 20 per cent of women with breast cancer. With partial mastectomy, the majority of patients also have a limited or complete axillary dissection for staging information. Although it may "cure" the occasional patient (remove the only metastasis), we do not believe that axillary dissection is curative, any more than dissection of the regional lymph nodes is curative in patients with cancer of other organs.

Our 5 and 10 year survival results of breast cancer at the Cleveland Clinic are given in Table 2. We have compared these results obtained in 710 patients from 1957 to 1970, with two other major published series of unselected patients with breast cancer treated by radical mastectomy during comparable time periods.[3, 4, 11, 12] The data from the National Surgical Adjuvant Breast Program (826 patients treated at 23 institutions in the United States) and the National Cancer Institute Cancer Registry (14,000 patients treated at six university hospitals and reported from three state cancer registries) (Table 3).[1, 6] The proportion of patients in Stages I and II in both of these series of patients is comparable to our patients at the Cleveland Clinic; 5 and 10 year survival results are similar.

During the past 15 years, there has been a decided trend away from radical mastectomy toward conservative operations for breast cancer in the United States, Canada, United Kingdom, and in Europe. Many institutions have now reported their results with the modified radical mastectomy in the treatment of breast cancer.

At Roswell Park Memorial Institute, beginning in 1969, modified radical mastectomy was used as the standard curative operative procedure for women with breast cancer. Nemoto and Dao[17] have reported on the early results of modified radical mastectomy and have compared the recurrence-free survival and the incidence of skin recurrences in patients after modified radical mastectomy to their earlier experience with radical mastectomy. They found no significant difference between the modified radical mastectomy and radical mastectomy.

At the Mayo Clinic, from 1965 to 1968, the results of modified radi-

cal mastectomy were compared with the results of standard radical mastectomy in 873 patients with breast cancer.[20] Five year survival was 70 per cent, essentially the same in both groups of patients, irrespective of the type of mastectomy performed when corrected for age and other prognostic factors. Similarly, at the Lahey Clinic, with well documented evidence that breast cancers are being diagnosed and treated at an earlier stage, a conservative but therapeutically graded approach to the treatment of breast cancer has been adopted, emphasizing modified radical mastectomy in the treatment of potentially curable breast cancer, utilizing adjuvant therapy for gradations in the stage of the disease.[2]

Handley[10] has reported from London 10 year survival results of 54 per cent in 425 patients with breast cancer after modified radical mastectomy, using the Patey technique with removal of the pectoralis minor muscle but preserving the pectoralis muscle.

Leis,[13] in New York, has reported on a series of 1298 patients with breast cancer treated by a selective surgical approach. He states that during the past 8 years, the modified radical mastectomy has become the most commonly performed procedure for invasive breast cancer; he now treats (1975) about 70 per cent of his patients with invasive breast cancer with modified radical mastectomy. He also reports a 10 year survival of 53 per cent for patients with Stages I and II breast cancer, with the selective surgical approach to breast cancer.

Papatestas and Lesnich[18] have compared radical mastectomy and modified radical mastectomy in 134 selected patients with carcinoma of the breast treated from 1964 to 1968. They found no essential difference in 5 year survival between the two groups, an average survival of 81 and 83 per cent, a high survival because of the exclusion of patients previously treated for other cancers or who had bilateral breast cancer.

Delarue and associates[5] have compared their early results with modified radical mastectomy in 100 consecutive patients with breast cancer at the Toronto General Hospital, 1950 to 1960, with those reported by the Ontario Cancer Institute for patients who had a standard radical mastectomy during the same period. The 5 year survival results were identical, 51 per cent, in both groups. Meyer, Smith, and Potter[16] have recently compared 1686 patients with carcinoma of the breast treated by modified radical mastectomy or radical mastectomy; there was no significant difference in 5 and 10 year survival between the two operative procedures.[16]

From these and other reports of comparison between the results of modified radical mastectomy and of standard radical mastectomy, it is apparent that the 5 and 10 year survival rates of the two procedures are comparable. Factors other than the operation performed are more important in determining whether patients with cancer of the breast will have long-term survival. Among these factors are the stage of the disease when the cancer is diagnosed, size of the lesion, age of the patient, and histopathologic type of the tumor. The surgeon, in selecting the operative procedure for treatment of the patient with breast

cancer, should therefore select that operation which will remove all evidence of local and regional disease while providing as good a cosmetic result as possible — one which will permit breast reconstruction at a later time for those women who may desire it. The modified radical mastectomy achieves this goal.

SUMMARY

The recent history of operations for breast cancer indicates a growing trend toward conservatism. The modified radical mastectomy achieves the goal of removing all evidence of cancer in the breast involved and removes the regional lymph nodes for accurate staging of the disease. In addition, it provides a cosmetic result superior to that of the standard radical mastectomy. Breast reconstruction may be undertaken at a later time with excellent results. The 5 and 10 year survival rates of comparable groups of patients after modified radical mastectomy and standard radical mastectomy appear to be almost identical.

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Indications for Radical and Extended Radical Mastectomy

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The selection of the surgical procedure for the primary treatment of women with potentially curable invasive breast carcinoma must be individualized. It should depend upon currently available data concerning the natural history of breast carcinoma, the histology, location, and extent of demonstrable disease as acquired by a structured, pretherapeutic evaluation of each patient. The decision-making process must be tempered by each patient's medical and emotional status. A data base derived from statistically sound reports of long-term survival patterns indicates that there are definable cadres of women whose best chance for long-term local control of disease are achieved by subjecting them to the standard radical or extended radical mastectomy. An attempt is made to dispel some of the confusion as to precisely what constitutes extended radical, standard radical, modified, and total mastectomies.

OBJECTIVES OF TREATMENT

A treatment regimen should provide a patient with the maximum chance for long-term survival with good quality of life. The gaps in our knowledge concerning breast carcinoma and the current limitations in our ability to define accurately the extent of disease prior to initiation of therapy must not deter us from utilizing available information. We must accept the concept that local control of disease, and even cure, may result only if the disease is limited to the breast, ipsilateral axillary nodes, and/or internal mammary nodes. Undetectable systemic spread of disease prior to therapy is common and results in the many treatment failures among women with so-called potentially curable breast carcinoma. The quality of survival not only depends upon the

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type of surgical procedure but, to a great degree, upon the patient's ability to readapt to society. Health professionals and other post-mastectomy patients are assuming a major role in helping women and their families cope with the physical, emotional, and economic problems resulting from their bout with cancer.

CONSIDERATIONS IN TREATMENT PLANNING

Nearly 80 per cent of women seeking medical assistance for a breast problem believe they may have breast cancer. Actually, cancer is found in less than 25 per cent of those subjected to biopsy. We surgeons have the responsibility of providing this and other pertinent information to our potential patients and their families prior to initiating diagnostic procedures and recommending specific operations. We must take the time to explain that a pre-therapy medical evaluation is essential. Medical deficits must be corrected. A conventional mammogram or xerogram is required in order to demonstrate the existence of nonpalpable lesions in the affected and/or the opposite breast. We must advise patients that mammograms are not always accurate and that a definitive diagnosis is established by the histologic analysis of the tumor mass by a pathologist. The frozen section procedure must be explained. It is prudent to comment on the paraffin section report which is forthcoming a few days after surgery is performed. We advise our patients that the entire surgical specimen is dissected and breast tissues and lymph nodes are studied by the pathologist. The specimens reported on frozen section as being benign are subjected to more detailed analysis. Occasionally there will be a small noninvasive or invasive carcinoma that was not found on frozen section. If these matters are explained prior to biopsy, the patient and her family will not assume that a mistake was made in reporting the frozen section as being benign when the occasional paraffin sections reveal carcinoma.

Pseudo-scientific articles on breast cancer in newspapers and magazines, discussions on talk shows on television and radio, and premature reports appearing in medical journals provide many women with information that prompts them to tell their surgeon what surgical procedure is indicated before he has had a chance to examine her and explain the rationale for the selection of the specific operation that she may need to provide her the maximum chance for long-term survival with good quality of life. It is imperative that he take the time to discuss the pretherapy work-up, the biopsy procedure, the importance of the type of carcinoma encountered, and the inability to demonstrate the existence of multiple foci of breast carcinoma in the breast until the total breast is examined histologically by the pathologist. The possibility of the spread of cancer to the pectoralis major fascia and muscle, to the lymph nodes beneath and between the pectoralis major and minor muscles, to the axillary nodes, and to the internal mammary nodes must be presented in language that she understands. In addition, we inform our patients that plastic reconstruction procedures are

available. We recommend that they be done several months after the primary surgery and only after the plastic surgeon has explained the contemplated procedure and what the patient may expect!

The gaps in our understanding of the behavior of a specific breast carcinoma must not deter us from utilizing the wealth of well documented data related to its genesis and patterns of growth. Foote and Stewart,[16] and Muir[31] independently described the multifocal origin of breast carcinoma over 30 years ago. This cannot be demonstrated prior to histologic analysis of the surgical specimen and only then if the responsible pathologist studies multiple sections of each specimen. The spread of breast carcinoma by lymphatic vessels to the axillary, internal mammary, and supraclavicular nodes is well documented. In addition, those nodes beneath the pectoralis major muscle and between the major and minor pectoral muscles are prone to metastatic involvement. Rodman,[40] Speese,[48] Ackerman,[1] Donegan and Sanders,[13] and others have reported on involvement of the pectoral fascia and muscle in significant numbers of patients whose primary tumors are located deep in the breast parenchyma. The probability of nodal involvement varies with the size of the primary tumor and the location and histology of the breast carcinoma. Consideration of all of these entities must be given when selecting a specific surgical procedure as the primary treatment intervention.

With few exceptions, surgeons do not perform the classic Halsted radical mastectomy. The clavicular head of the pectoralis major is preserved and few surgeons find it necessary to utilize a skin graft for primary closure of the wound. Modifications of the classic transverse incision have, in general, replaced the vertical incision, except in those unusual situations in which the dominant tumor mass is located in the upper inner or extreme upper outer quadrant of the breast. The standard radical mastectomy results in the removal of a block of tissue which includes a generous segment of the skin of the breast including the areola and nipple, all breast tissue including the infraclavicular segment, the pectoralis major fascia and muscle (with preservation of its clavicular head), the lymph nodes and fat beneath the major and between the major and minor muscles, the pectoralis minor muscle, and the fat and nodes inferior to the major axillary vessels and nerves. Skin grafts are used less than 5 per cent of the time at our institution.

Unfortunately, a modified radical mastectomy means different things to many surgeons. The Patey mastectomy preserves the pectoralis major muscle and its nerve. The specimen includes all other tissues removed by a standard radical mastectomy. A skin graft is rarely, if ever, used. At times, a segment of the pectoralis major muscle directly beneath the dominant mass is included in the surgical specimen. Although not reported in the literature, this is frequently done if the cancer is located deep in the breast parenchyma or is over 2 cm in its greatest diameter. Scanlon utilizes a modification of the standard radical mastectomy by detaching the major and minor muscles from the chest wall, preserving their nerve supplies, and then reuniting them during the closure of the wound. This maneuver enhances the removal of the subpectoral and axillary nodes and fat.

Others, including Auchencloss, preserve the pectoralis muscles and their nerve supplies. They augment their exposure of the axilla by draping the arm free, thus enabling them to elevate the arm during the dissection of the contents of the axilla. The surgical specimen includes the fascia of the pectoralis major, the fat and nodes beneath the major and between the major and minor, and the axillary fat and nodes. At times these surgeons resect the inferior segment of the major muscle, thus providing a greater margin of tissue beneath the dominant mass.

Unfortunately, there is another group of surgeons who perform what Coller designated as a "Blue Shield Mastectomy." This inadequate procedure provides the pathologist with some skin, the nipple and areola, and a few lymph nodes, while the patient retains varying amounts of breast parenchyma, microscopic foci of breast cancer, subpectoral nodes and fat, and an undetermined number of axillary lymph nodes, some of which may well contain micro- and macro-metastates of breast carcinoma.

The existence of direct lymphatic channels coursing from the breast to the internal mammary nodes was demonstrated long before Halsted popularized the radical mastectomy as the procedure of choice in treating women with potentially curable breast carcinoma. Subsequently, Handley, Deaver,[12] Rodman,[40] and Stibbe reported on the accessibility to operation without undue risk to the pleura. However, surgical opinion was not in favor of internal mammary node removal as a routine measure in operations for breast carcinoma.

In 1952, Urban and Baker[54] reported on the effects of including the en bloc resection of the internal mammary lymph nodes while performing the standard radical mastectomy on women with invasive breast carcinomas located in the central and medial quadrants of the breast. Subsequently, Urban and associates have reported on long-term survivals of these cadres of women. As compared with the results following radical mastectomy, Urban's patients have fewer local recurrences, longer survivals, and approximately the same morbidity and surgical mortality.[52, 56] His surgical technique is superb. The surgical specimens include an en bloc segment of overlying portions of ribs, the internal mammary chain of nodes and blood vessels, and the underlying pleura. The procedure takes between two and one half and three hours. Patients are usually discharged on the seventh or eighth postoperative day as compared with discharge on the sixth or seventh day for standard or modified radical mastectomy. Patients subjected to radical mastectomy achieve similar range of motion of the ipsilateral arm and readapt to society in approximately the same length of time as that noted for women subjected to less radical procedures. Urban's contraindications for this procedure are limited to women of advanced age, those with marked medical deficits, and those with noninvasive or histologically low-grade invasive carcinomas. Patients with lesions less than 1 cm in diameter are subjected to biopsy of the internal mammary nodes. If this proves negative, only a standard radical mastectomy is performed.

In 1974, Livingston and Arlen[28] reported on their series of 583 patients who underwent extrapleural extended radical mastectomy during the years 1955 through 1970. Of the 296 patients with other quadrant lesions, 5 per cent (8 patients) had positive internal mammary nodes and negative axillary nodes. Twenty-three per cent (30 patients) had positive axillary and internal mammary nodes, for an overall incidence of 13 per cent among women with outer quadrant lesions. Among the patients with inner quadrant lesions, 14 per cent (70 patients) of the patients with negative axillary nodes had positive internal mammary nodes. Patients with inner quadrant lesions and positive axillary nodes (27) were reported to have internal nodal involvement 59 per cent (16) of the time. The centrally located lesions were associated with a 10 per cent internal mammary nodal involvement if the axillary nodes were not involved and a 43 per cent internal mammary node involvement if the axillary nodes were involved. If the dominant lesion involved the nipple, and the axillary nodes were positive (11 patients), the internal mammary nodes contained metastases in 63 per cent of patients. Patients with nipple lesions and negative axillary nodes (26 patients) had no internal mammary nodal involvement.

Veronesi, Caseres,[6] Margottini,[29] and Koszerowsky have reported 5 and 10 year survival rates similar to those of Urban and Livingston. The majority of the critics of the extended radical mastectomy present the results of Dahl-Iversonand and Johansen, both of whom do not perform en bloc dissections. Their operating time is approximately one hour. Their local recurrence rates are high and their salvage rates are poor. It seems rather unfair that the splendid works of Veronesi, Caseres, Margottini, and Koszerowsky are not mentioned by the opponents of the extended radical mastectomy.

Urban's and Livingston's reports clearly demonstrate the probability of internal mammary nodal involvement with central and medial lesions, especially if axillary nodes contain metastases. Livingston's report on internal mammary nodal involvement among patients with outer quadrant lesions and positive axillary nodes (43 per cent) provides an added dimension in treatment planning. Adjunctive radiation therapy to the internal mammary nodal area should be seriously considered in these cadres of patients if en bloc resection of the internal mammary chain of nodes is not performed. Adjunctive radiation therapy is recommended in those patients with positive internal mammary and/or axillary nodes. This prophylactic supravoltage therapy is given to the base of the neck and the internal mammary area. It is also applied to the chest wall when the primary lesion is large, and extensive axillary and/or internal mammary nodal involvement has been demonstrated. We are involved in controlled clinical trials using adjunctive chemotherapy but will not recommend these regimens as standard treatment until they have been proved to increase long-term survival. A great need exists for systemic therapy that will destroy undetected systemic disease at the time of primary treatment. Currently, adjunctive therapy under investigation is not free of sequelae and has not provided solid data that demonstrate an increase in the quality of duration of survival.

SUPPORTIVE POSTOPERATIVE CARE

Much has been made of the improved quality of survival of patients who have been subjected to surgery of less magnitude than to the standard radical mastectomy. A perusal of the literature does not substantiate this empirical observation. Our own experience certainly negates this belief. For the past 30 years the professional staff at Memorial Hospital has provided structured rehabilitation programs for our mastectomy patients. These efforts have been implemented by the multidisciplinary input of surgeons, physiatrists, psychiatrists, nurses, physical therapists, social workers, and post-mastectomy volunteers and their husbands. Evaluation of our efforts to readapt post-mastectomy patients to society during the past eight years indicates that the majority of women have returned to their pretherapy status emotionally and physically within eight weeks. The data reflect very little difference among patients following modified, standard, or extended radical mastectomy. Those patients whose nerve supply to the pectoralis minor was destroyed while preserving this muscle had greater limitation of shoulder motion than women subjected tothe standard radical or extended radical. We believe that the use of the Hemovac drainage system has enhanced wound healing and arm function.

Emotional support programs provided prior to and following surgery by our office and hospital staffs have evolved as the result of structured educational efforts supported by our administrators, health professionals, and the American Cancer Society's Reach to Recovery volunteers. We provide our patients with a five minute recording prior to hospital admission. The record contains pertinent information regarding their hospital admission and enables the family and the patient to acquire an overview of events to come. The surgeon and his office staff have explained these matters to the patient while in the office, but we recognize that these women are so distraught that recapitulation of pertinent information is most helpful.

During their hospital stay our patients are involved in structured exercise classes, discussion sessions with nurses, physical therapists, social workers, post-mastectomy volunteers and their husbands and, in addition, psychiatrists, if indicated. Measures to prevent hand and arm swelling, prosthetic appliances, plastic surgery, clothes, family and sexual problems, the use of adjunctive therapy, and follow-up care are discussed. A booklet prepared jointly by the New York City Division of the American Cancer Society and the Staff of Memorial Hospital and a phonograph record containing a discussion between three long-term post-mastectomy patients, a nurse, and a staff surgeon of the Breast Service are supplied to each patient prior to discharge. These contain much of the information acquired by the patient during her hospital stay. We have observed that patients are quite tense and forget suggestions unless they are repeated and augmented by audiovisual aids. The insurance carriers, after a modicum of resistance, have assumed the cost of this program for our patients.

STATISTICS RELATED TO LONG-TERM SURVIVAL OF PATIENTS WITH POTENTIALLY CURABLE BREAST CARCINOMA

The devious ways that statistics are presented by investigators is an enigma to physicians who are honestly striving to choose the most effective treatment regimen available for the management of women with potentially curable breast carcinoma. Editors of medical journals rarely set down criteria for reporting data. Hence, survivals may be reported by the crude, relative, or actuarial methods, or even by the Gage-Berksen method, which records the total experience in a given time period, accepting the fact that at the end of that period many of the patients were treated three or four years prior to the end of the total years studied. Certain formulas are utilized which are reputed to be statistically sound. The chance of presenting a fair analysis frequently is negated by reporting the data of the investigator who has utilized a different and usually more extensive procedure by the crude, relative, or actuarial methods in which all patients were treated for, say, 10 years, not during a 10 year period.

Another deterrent to comparative analysis is the so-called randomized study. A comparison of results should involve patients with similar stages of disease: same size of tumors, number and level of nodes involved, quadrant location of the dominant mass, and histology of the carcinoma. There should be quality control of the surgery and gross and histologic analysis of the surgical specimens. The multi-institutional studies frequently have little, if any, quality control, and frequently do not meet the criteria for randomized studies. Reporting short-term survival figures does not reflect meaningful results of one's efforts to control local disease or produce a cure. Most investigators now accept a 10 year follow-up as a minimum time span of surveillance.

Significant differences exist in the definitions of what cadres of women are considered to be potentially curable. One is assured of superior results if he considers 25 to 50 per cent of his patients as being operable. However, Adair, Leis, and many other surgeons regard 90 per cent of their patient population as being potentially curable. Thus, uniform classification and staging of the extent of disease are essential if statistics are to have any semblance of validity.

Inasmuch as local control of disease is all that surgeons and radiation therapists can achieve, there should be a standard method of reporting local recurrences. Unfortunately, this is not the case. Some investigators do not consider axillary recurrences to be local recurrences. Some report the demonstration of carcinoma in a breast following a partial mastectomy or in a therapeutically radiated breast after biopsy or partial mastectomy as evidence of a new cancer, not as a recurrence. Because of any or all of these practices, confusion exists in the minds of many surgeons concerning the best way to treat a woman with potentially curable breast carcinoma.

DISCUSSION

The staff of the Breast Service of the Department of Surgery at Memorial Hospital performed over 700 mastectomies in 1977 for noninvasive and invasive carcinoma in women judged to have potentially curable breast carcinoma according to our criteria of operability. This constituted approximately 94 per cent of our total breast carcinoma population. Modified radical mastectomies were performed on 45 per cent of our patients. In 1967 only 16 per cent of our patients received modified radical mastectomies. We are seeing more patients with noninvasive carcinomas and small invasive carcinomas (< 1 to 2 cm). Patients with deep seated small lesions frequently had the inferior two-thirds of the pectoral major removed, but the operation was designated as a modified radical mastectomy; the nerve and blood supply to the major muscle were preserved. The pectoralis minor muscle and its nerve and blood supply were preserved. At times the pectoralis minor muscle is resected (Patey operation). The surgical specimens from both types of procedures contain similar numbers of axillary nodes (20 to 25). When the minor muscle is preserved, the arm is draped free, thus providing improved exposure. The fat and nodes beneath and between the two muscles are removed.

Unfortunately there are many patients who do not come to definitive surgery until the dominant mass is over 2 cm in diameter. We have observed that there is a 60 per cent incidence of positive lymph nodes in this latter cadre of patients compared with a 38 per cent involvement among women with small lesions. Unfortunately, women with large cancers have a much greater percentage of positive nodes at levels 2 and 3 than those patients with small lesions. We believe that these women should be given the benefit of a more extensive nodal dissection plus the removal of the muscles and their lymphatic vessels — a standard radical mastectomy or, for specified patients, an extended radical mastectomy. Deposits of metastatic carcinoma have been observed in the retained muscles by the author and other surgeons when a modified radical mastectomy served as the primary therapy for women with Stages II and III breast carcinomas.

SUMMARY

The choice of a surgical procedure for patients with potentially curable breast carcinoma must be individualized. With the increase in the number of women presenting noninvasive carcinomas, preclinical invasive carcinomas (< 0.5 cm), and lesions less than 2 cm in diameter, a modified radical mastectomy is an acceptable and adequate procedure for achieving local control of disease.

When the primary lesion is deep seated or is greater than 1 cm in diameter, it is prudent to resect the inferior portion of the pectoralis major muscle as part of the modified radical mastectomy.

The lymphatic drainage of the breast to the axilla, through the

pectoralis major muscle, to the internal mammary lymph nodes, the subpectoralis major nodes, and the nodes between the major and minor muscles should be considered in planning a treatment regimen for women with potentially curable breast carcinoma.

The standard radical mastectomy is indicated when patients have large primary lesions and/or extensive axillary node involvement.

The extended radical mastectomy is recommended for women with inner quadrant and centrally located primary lesions in order to remove the internal mammary nodes. If for medical or other reasons an extended radical mastectomy is not recommended for this cadre of patients, radiation therapy to the internal mammary and supraclavicular areas is believed to be a reasonable substitution.

ACKNOWLEDGMENT

The author acknowledges the assistance of Drs. George Degenshein, Brooklyn, New York, and George Sanders, Louisville, Kentucky, for their assistance in furnishing valuable data relating to the lymphatic drainage of the breast as it reflects upon the deposits of metastatic breast cancer in the fascia and muscles of the chest wall.

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Primary Radiation Therapy for Operable Carcinoma of the Breast

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The hope of finding a substitute for mastectomy in treatment of breast cancer has been discussed in the medical literature for many years. Geoffrey Keynes, a British surgeon, wrote in 1937: "I feel it must be the ambition of every conscientious surgeon to assist in the gradual elimination of any operation so extensive and severe as the radical operation for cancer of the breast."[4] Keynes treated his first patient with radium needles following local excision in 1924 and, in 1937, reported the results of this treatment in 250 patients. Despite his report of survival comparable to that attained by his surgical colleagues, little interest in the technique was engendered. In the ensuing decades, the development of the radiation therapy of breast cancer was hampered by the availability of only comparatively low energy radiation for therapeutic use resulting in severe skin reactions and cosmetically unacceptable changes in breasts so treated. Baclesse[2] in 1949 called attention to the fact that with adequate protraction, radiation therapy could result in cure of breast cancer without severe radiation injury.

The advent of megavoltage radiation therapy equipment has allowed the possibility that radiation therapy will become an acceptable substitute for mastectomy. Following the lead of Baclesse, Pierquin and his colleagues in six French cancer centers began treating "operable" breast cancer with primary radiation therapy in 1960, and in a recent publication reported excellent local control and survival in 310

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patients who were followed for periods of 3 and 5 years.[7] Other reports of primary radiation therapy from both this country and abroad may be found in the literature.[5, 6, 8, 9]

In 1972, a report of a controlled clinical trial comparing radical mastectomy with wide excision appeared in the literature.[1] Both groups of patients received radiation therapy postoperatively. This report by Sir Hedley Atkins and colleagues has been cited as demonstrating the superiority of radical mastectomy over "tylectomy" plus radiation therapy, with the former group demonstrating a lower local recurrence rate in both Stages I and II and a better survival in Stage II. Unfortunately, the doses of radiation therapy chosen were far from adequate. Orthovoltage radiation was employed in the treatment of the axilla, and the appearance of moist desquamation limited the dose to a maximum of 2700 rads in 18 days. The breast was treated with 6 Mev (megavoltage) of radiation, but because full bolus was employed to build up the skin dose, the total dose to the breast was limited by skin reaction to a maximum of 3800 rads in 3 weeks. With radiation techniques and doses such as these, one can well anticipate a substantial local recurrence rate as well as less than ideal cosmetic results.

SERIES STUDIED BY THE JOINT CENTER FOR RADIATION THERAPY

At the Joint Center for Radiation Therapy, the treatment of breast cancer utilizing radiation therapy as the primary modality was begun in July, 1968; 129 patients with Stages I and II disease have been treated through December, 1976. The composition of this group of patients together with the range of follow-up is shown in Table 1. Six patients required treatment of both breasts, either because of simultaneous (two) or sequential tumors (four), making a total of 135 breasts treated.

Currently, prior to the start of radiation therapy, an excisional biopsy is performed to establish the diagnosis and reduce the number of tumor cells that must be destroyed by irradiation. In those instances in which excision is not feasible, incisional biopsy or needle biopsy is

Table 1. *Patients with Stages I and II Breast Cancer Treated Between July 1968 and December 1976 by the Joint Center for Radiation Therapy*

TNM CATEGORY	STAGE	NO. OF PATIENTS	BILATERAL TUMORS	RANGE OF FOLLOW-UP
T_1, N_0	I	45	2	11 to 89 months
T_2, N_0	II	52	2	
T_1, N_1	II	14	1	12 to 97 months
T_2, N_1	II	18	1	
TOTAL		129	6	11 to 97 months

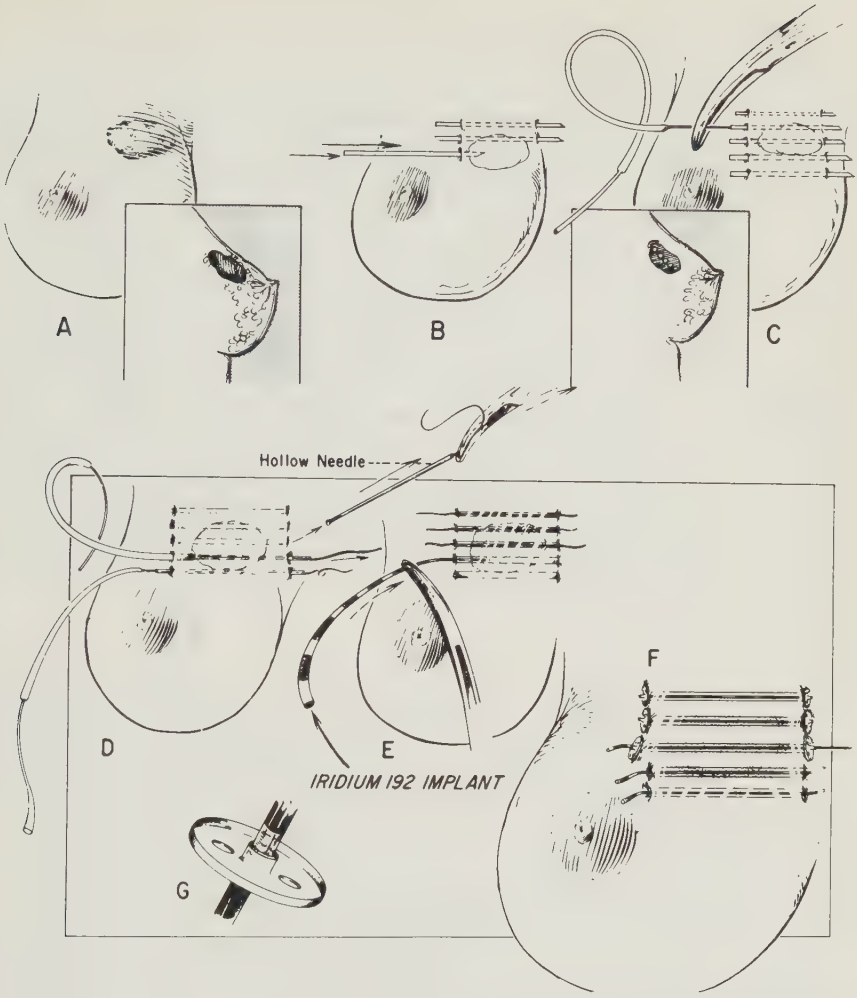

Figure 1. *A*, Tumor in the breast. *B*, Implantation with hollow needles. *C* and *D*, Needles replaced by nylon tubing. *E* and *F*, ^{192}Iridium inserted into the tubing.

used to establish the diagnosis. No attempt is made to achieve wide excision. We have found in analyzing the cosmetic results in patients treated by primary radiation therapy that the location and extent of the biopsy are significant in the ultimate appearance of the treated breast. Circumareolar biopsy incisions are to be preferred, and the volume of tissue removed should be kept to the minimum necessary for gross excision of the mass. In recent years, we have been employing a small low axillary incision to sample axillary nodes in premenopausal women to aid in determining the need for adjuvant chemotherapy. It is important that the procedure be kept to a small sampling operation

since extensive dissection when combined with irradiation may result in breast or arm edema.

Our radiation therapy techniques have gradually evolved during this period. We currently employ external beam irradiation utilizing a 4 Mev linear accelerator to deliver a dose to the breast of 5000 rads. Clinically negative lymph node regions receive 4600 rads. Tangential fields treat the breast and ipsilateral internal mammary nodes while minimizing the volume of lung irradiated. The supraclavicular and axillary nodes are treated by an anterior field. It is quite important that bolus is not employed so that the skin dose is kept as low as possible, and wedges are used as compensators to prevent overdosing the distal portion of the breast. Patients are treated five times a week and receive 200 rads per fraction. About two weeks after completion of the external beam therapy, the site of the primary tumor is implanted with radioactive ^{192}iridium seeds using an afterloading technique. The method is illustrated in Figure 1, showing how 18 gauge long needles are used to introduce polyethylene tubes that serve as a receptacle for the ^{192}Ir. The procedure is usually performed under general anesthesia, but local anesthesia may be used when the former is contraindicated. Doses of 1500 to 3000 rads are usually delivered with the iridium implant at approximately 40 rads per hour.

Results

Both radiation therapy and surgery are local treatments, and therefore their success must be determined by controlling the tumor in the primary or the regional volume. Thus far, there have been 7 patients with local failure in the 135 treated breasts, 1 of 45 Stage I and 6 of 84 Stage II breasts. The cumulative likelihood of local control is shown in Figure 2 and is 94 per cent at 5 years for Stage I and 86 per cent for Stage II. During the evolution of our current technique, we have learned the value of interstitial implant and excisional biopsy. Figure 3 shows the local control in those patients implanted as compared with those receiving external radiation only. Thus far, no local failures have occurred in implanted patients. Table 2 demonstrates that excisional biopsy similarly reduces recurrence as compared with needle or incisional biopsy.

Survival data are in our judgment of less importance in evaluating these techniques since survival largely depends upon whether or not there are preexisting subclinical metastases at the time of initial diagnosis. Figure 4 presents our actuarial survival, indicating a 91 per cent 5 year survival for Stage I and 66 per cent for Stage II.

The majority of complications (Table 3) have been minor and have not required hospitalization or surgery. Rib fractures have been the most common complication; all have healed uneventfully and have become asymptomatic. The only major complication occurred in one patient who developed a pericardial effusion that required surgical treatment with a pericardial window. This patient had received treatment to both breasts for bilateral tumors. The treatment technique used in irradiating both internal mammary chains is a modification of our

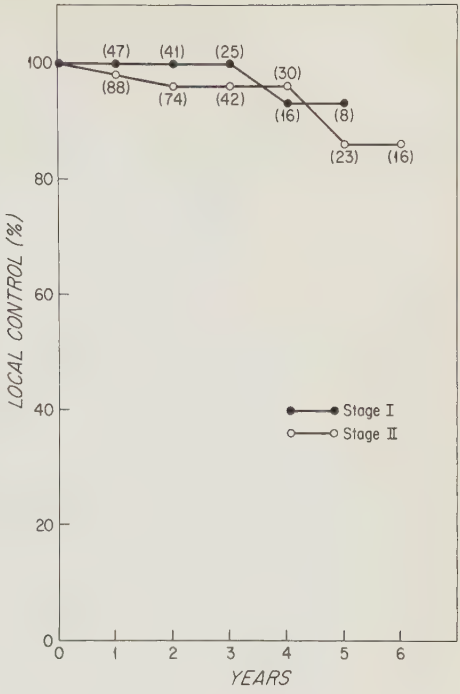

Figure 2. Cumulative probability of local control of Stages I and II breast cancer is shown. This includes breast and regional draining lymph nodes.

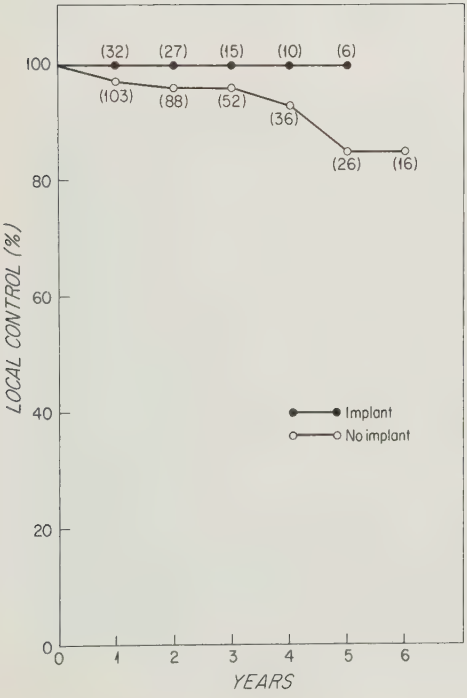

Figure 3. Cumulative probability of local control in patients who did or did not receive a "boost" ^{192}iridium implant is shown.

Table 2. *Incidence of Local Recurrence**

BIOPSY PROCEDURE	LOCAL RECURRENCE	NO. TREATED
Excision	4	118
Less than excision	3	17

*The difference in these proportions is statistically significant ($P < .05$).

standard technique and gave a significant dose of radiation to the pericardium.

We have studied the cosmetic results in patients with Stages I and II carcinoma of the breast treated by primary radiation therapy in order to identify those factors that influence the final appearance of the treated breast. We have been able to determine three factors that play an important role in the end cosmetic result: the nature of the biopsy procedure, the radiation fractionation and total dose, and the technique of delivery of the radiation therapy. Figures 5 to 7 are examples of a few of our patients in whom the cosmetic and functional results have been acceptable.

The surgeon about to obtain a biopsy of a breast that may be treated primarily by radiation therapy should seek to keep the surgical scar as inobtrusive as possible. A circumareolar incision, when feasible, is

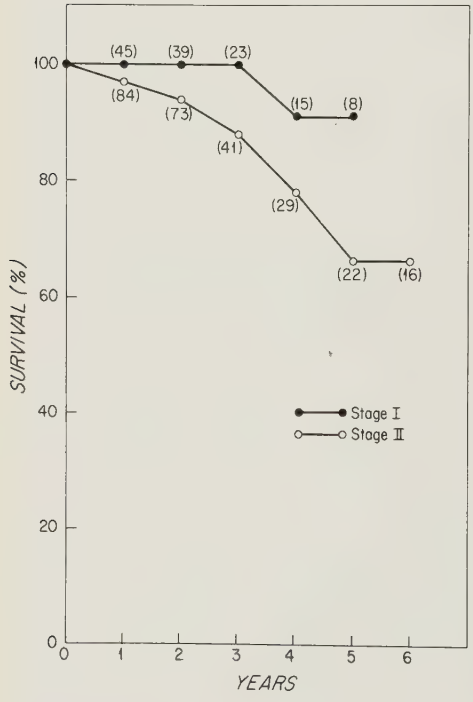

Figure 4. Cumulative probability of survival in Stages I and II breast cancer is shown.

Table 3. *Complications of Radiation Therapy*

Minor (No hospitalization or surgery required)	
Rib fractures	8
Pulmonary reaction	3
Pleural effusion	1
SUBTOTAL	12 (16 per cent)
Major	
Pericardial reaction	1 (1 per cent)
TOTAL	13 (17 per cent)

preferred. The amount of tissue removed is also important since attempts at wide local excision can lead to excessive deformity. An excisional biopsy need remove little more than the gross tumor.

Radiation dosage, particularly that delivered by external beam irradiation, is important. Six patients who received external beam doses of 6000 rads showed significant fibrosis, whereas those receiving 5000 rads rarely showed recognizable changes. The local dose can be boosted by interstitial implantation without damaging the cosmetic result.

The technique of delivery of the external beam of radiation is the third factor influencing the final cosmetic result. Meticulous technique is required with avoidance of overlapping fields due to divergence of the x-ray beam, the use of proper wedges as compensators to reduce dose inhomogeneity, and the avoidance of use of bolus. Bolus has been traditionally used in treating breast cancer deliberately to abrogate the skin-sparing effect of megavoltage radiation. However, since the superficial skin is rarely involved in early breast cancer, bolus should be

Figure 5. Patient with Stage I carcinoma of the left breast treated 30 months before photograph.

Figure 6. Patient with Stage II carcinoma of the left breast treated 33 months before photograph.

Figure 7. Patient with Stage I carcinoma of the right breast treated 48 months before photograph.

dispensed with and advantage taken of the superior cosmetic result achieved when the dose to the skin is kept to a minimum. Technical details concerning the dose distribution in the skin may be found in a paper by Svensson et al.[10]

Discussion

William Halstead in 1894 reported on the surgical treatment of 50 cases of breast cancer and pointed out that, "The efficiency of an operation is measured truer in terms of local recurrence than ultimate cure."[3] This is even more apparent today when the treatment for many patients with early carcinoma of the breast devolves into two phases, the first dealing with local disease, e.g., the breast and regional lymph nodes, and the second with the prevention of distant metastases. The comparison between surgical treatment and radiation treatment is, therefore, best made by examining local control figures in Stages I and II disease. Our own experience with 1 local failure in 45 treated breasts in Stage I, and 6 local failures in 84 treated breasts in Stage II, is borne out by other series using radiation treatment. For example, Pierquin and colleagues[8] reported only 3 local recurrences in T_1 and T_2 lesions in 108 patients followed for 3 years. Spitalier et al.[9] observed 11 local recurrences in 160 patients (8.8%) with Stages I and II breast carcinoma with 5 years of follow-up. Prosnitz and others[8] assembled a series of 150 patients with Stages I and II disease treated at four institutions. It should be pointed out that 57 of these patients are from the current series of the Joint Center for Radiation Therapy. The local recurrence for this gorup of patients was 10 (6.6 per cent). Both Spitalier and Prosnitz found that in the event of local failure, 50 per cent of patients could still achieve local control by mastectomy. Peters[6] has reported a matched pair analysis of 145 patients treated by local excision and radiation therapy, with follow-up ranging from 6 to 30 years. These patients are compared for local recurrence with a similar group treated by mastectomy and postoperative radiation therapy. In each group, the rate of local recurrence was 7 per cent.

In those institutions in which a decision is made to offer this alternative form of therapy to women with breast cancer, it is important that a good working relationship be developed between the surgeon and radiation therapist. Consultation between services prior to biopsy is essential and all concerned must have an opportunity to examine the patient. A mutual decision must be made concerning the extent of the biopsy, the need for axillary sampling and its extent, and in certain instances the need for specimen mammography to determine the adequacy of the excision.

It is our belief, on the basis of available data, that the primary radiation therapy of breast cancer following local excision is an acceptable alternative to mastectomy, which can be offered to patients without seriously altering their chances to achieve local control, and with superior cosmetic results. As in the patient treated by mastectomy, consideration must also be given to the employment of systemic chemotherapeutic agents for control of occult disseminated disease.

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Current Use of Steroid Hormone Receptor Assays in the Treatment of Breast Cancer

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Breast cancer is the leading cause of cancer death in women today. Although more than 90,000 new cases are diagnosed and 30,000 women die annually from breast cancer, few major advances have occurred in our understanding of the disease or its treatment until recently. In the past few years, however, basic laboratory research into the factors controlling breast cancer cell growth has been rewarded with significant new information applicable to the clinical care of patients. In fact, as a direct result of laboratory investigation, our approach to the management of this malignancy has changed dramatically.

This is especially true for our understanding of the hormone dependence of breast cancer. It has been known for nearly a century that alteration of the hormonal milieu causes tumor regression in certain women with metastatic breast cancer. This observation is not surprising, since growth of the normal mammary gland is influenced by a variety of hormones. However, only about 30 per cent of women with breast cancer respond to modern hormonal manipulation, and the mechanism for the response is poorly understood.

Because of this relatively low response rate to endocrine therapy, combination chemotherapy with cytotoxic agents has become increasingly popular as the primary therapy for metastatic disease. Sixty to seventy per cent of patients now respond to chemotherapy with median durations of remission approaching one year. Yet such therapy is not without significant morbidity and occasional mortality. Furthermore, those patients who might have had a durable remission with a simpler, less toxic endocrine therapy are excluded by this approach.

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Thus, an accurate method of determining a priori which patients are better suited for chemotherapy and which patients are better candidates for hormonal manipulation is highly desirable. Accurate selection of appropriate therapy would minimize the number of patients exposed to toxic chemotherapy or hazardous endocrine ablative procedures when such treatments are likely to be ineffective.

Clinical criteria such as menopausal status, sites of tumor involvement, and disease-free interval after surgery have not significantly improved the clinician's ability to select appropriate therapy. Recently, however, basic research into the biochemical mechanisms of hormone action in breast cancer has resulted in an accurate method of selecting breast cancer patients likely to respond to hormone therapy. Data from a variety of laboratories has confirmed that measurement of estrogen receptor protein (ER) in biopsy specimens is a useful marker of hormone dependence or independence of a patient's tumor.[9] In addition, evidence is mounting that ER is an important prognostic variable, providing information about the natural history and biology of the tumor and clues to new treatment strategies.

In this article we will review the current status of the use of ER assays in the management of patients with breast cancer. In addition we will discuss the use of other biochemical techniques to improve further the accuracy of this assay. Finally, we will briefly discuss antiestrogens, a group of drugs providing a useful addition to the armamentarium of the oncologist.

BIOCHEMISTRY OF HORMONE-DEPENDENT BREAST CANCER

Nearly 20 years ago it was observed that radioisotopically labeled estrogens injected in vivo localized in normal target tissues.[3] Soon after, studies in experimental animals and humans with breast cancer demonstrated that labeled estrogens also localized in breast tumor tissue.[2] Furthermore, hormone-dependent tumors, those which responded to endocrine therapy, concentrated more estrogen than hormone-independent tumors.[5] A plausible explanation for these observations arose with the discovery that a cytoplasmic protein, the estrogen receptor, was responsible for the specific uptake of estrogen by both normal target tissues and breast cancer.[4]

Subsequent studies in recent years have given rise to a model of the biochemical mechanism of steroid hormone action shown schematically in Figure 1. The hormone readily diffuses across the cell membrane where it is trapped and concentrated in those cells containing specific high affinity receptors. The receptor-hormone complexes then translocate to the cell nuclei and bind to chromatin. By unknown mechanisms transcription of specific mRNA and subsequent synthesis of specific proteins are altered, resulting in a biologic effect. Absence of the hormone receptor or a defect in the sequence of events subsequent to binding results in the inability of the cell to respond to the

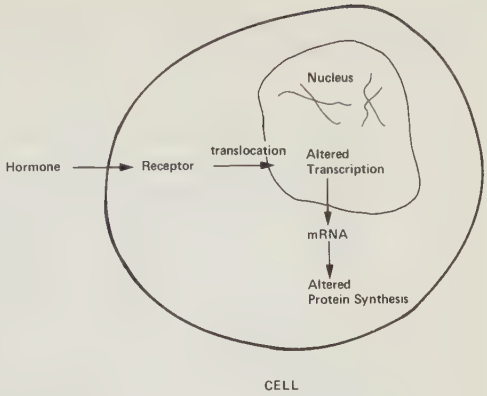

Figure 1. Mechanism of steroid hormone action.

hormone. Thus, the absence of estrogen receptor in breast cancer cells should preclude any direct effects of estrogens on the tumor.

The discovery of the estrogen receptor protein led to the proposal that measurement of the receptor in biopsy specimens might predict the hormone dependence of the tumor. Several techniques were developed to measure ER in human breast cancer specimens. In 1974 an international workshop was held to review the results from several laboratories attempting to correlate tumor regression following endocrine therapy with the ER assay. Despite differences in methodology, these laboratories produced consistent results, clearly demonstrating that the ER assay was valuable in predicting response to endocrine therapy in patients with metastatic breast cancer.[9]

ESTROGEN RECEPTORS IN HUMAN BREAST CANCER

Estrogen receptors in human breast cancer, as in other target tissues, demonstrate high affinity and remarkable steroid specificity for estrogenic hormones. The concentration of ER in tumor specimens varies over a wide range (0 to more than 1000 fmol per mg cytoplasmic protein). This variation has been attributed in part to tumor cell heterogeneity where the ER value varies with the proportion of tumor cells that contain receptor. The level of endogenous estrogen may also influence the ER determination, since high levels of hormone might mask receptor sites, making them unavailable for assay, or might translocate cytosol receptors to the nucleus where they will not be measured by conventional techniques. This factor may partially explain the relationship between age or menopausal status and ER concentration. Several studies have confirmed that postmenopausal women with reduced estrogen levels have a greater proportion of ER positive tumors and higher ER concentrations.

Tumor ER levels may also depend on the type of tissue obtained for assay. Tissue from primary breast tumors is more often receptor

positive (77 per cent) than that from metastatic tumors (66 per cent).[8] One possible explanation is that tumor cells may become more undifferentiated and lose normal endocrine control mechanisms as the disease progresses. In addition, if the primary tumor were composed of both ER positive and negative cells, the hormone independent (ER negative) cells could become dominant due to favorable growth kinetics or other biological advantages. In fact, ER negative cells tend to have a higher labeling index and growth fraction than ER positive cells, suggesting a more rapid proliferative capacity.[11] Preliminary data from a few patients having multiple sequential biopsies showing a progressive decline in ER level with time support this notion.[13] The effect of endocrine or chemotherapy on tumor ER is not known; nor is there sufficient information regarding ER levels in simultaneous tumor biopsies from different sites in the same patient to draw firm conclusions. In any event, because of the potential for change in the ER status of a tumor with time, it is prudent, if possible, to obtain tissue for assay just prior to instituting treatment.

Preliminary evidence suggests that estrogen receptor content does correlate with certain histologic features of the breast tumor.[9] High grade or more undifferentiated tumors tend to have a greater proportion of ER negative assays. Recently a high frequency of ER positive assays has been described in lobular carcinoma, and tumors with a prominent local lymphocyte reaction are more frequently ER negative.[12] The lack of correlation between tumor response to endocrine therapy and tumor morphology reported in the older literature raises suspicion concerning the validity of these data. Several ongoing studies comparing morphology with results of ER assay in large numbers of patients should answer these important questions.

Other parameters such as clinical stage of disease, axillary nodal status, tumor size and tumor location in the breast do not correlate with the presence of ER. As discussed below, the response to endocrine therapy (but not the duration of response) correlates with the ER concentration.

CORRELATION OF ER WITH RESPONSE TO ENDOCRINE THERAPY

Tumor ER status correlates well with response to hormone therapy (Table 1). These collective data from over 400 treatment trials from 14 institutions using different ER assay methods were presented at the international workshop on estrogen receptors four years ago.[9] Clinical correlations were evaluated by independent reviewers, and the general pattern of results has been confirmed by subsequent independent studies. Tumors containing ER have a 55 to 60 per cent response rate to ablative and additive endocrine therapies. Although this correlation is not dramatic, the response rate is double that seen when patients are selected by the usual clinical criteria alone. A more striking relationship is observed for ER negative tumors. Less than 10 per cent of

Table 1. *ER Status and Response to Endocrine Treatment*

THERAPY	ER+	ER−
Ablative	55/99 (55%)	8/86 (9%)
Ovariectomy	23/33	4/53
Adrenalectomy	32/66	4/33
Additive	51/85 (60%)	7/82 (8%)
Estrogens	37/57	5/58
Androgens	12/26	2/24
Glucocorticoids	2/2	–

these patients have objective remissions with endocrine therapy. It is important to emphasize that the ER status is useful in predicting response to any hormonal manipulation including hypophysectomy and antiestrogen treatment. Since the mechanism by which some forms of endocrine therapy induce tumor regression is not clear and may not be due only to changes in estrogen levels, ER may simply be serving as a marker of tumor differentiation. Perhaps more differentiated tumors retain the ability to respond to a variety of changes in the hormonal milieu.

It is clear that the ER assay is most helpful when the tumor is receptor negative. Clinicians can exclude with considerable confidence those patients with negative assays from any endocrine therapy. On the other hand, whereas a positive ER assay significantly improves the clinician's ability to select patients likely to respond to endocrine therapy, about one-third of these tumors fail to respond. Recent studies (discussed below) have explored possible ways of increasing the accuracy of the ER assay in the receptor positive group of tumors.

Quantitative ER Levels

If breast tumors contain variable proportions of ER positive and negative cells, one might expect that tumors with more ER positive cells and, thus, a higher absolute ER level might be more responsive to endocrine therapy. Although preliminary observations did not reveal a correlation between the level of ER and response to therapy,[9] our most recent analysis of 111 patients with receptor assays on metastatic biopsies who have undergone various endocrine therapies supports this hypothesis (Table 2).[10] Only 6 per cent of tumors with absent or

Table 2. *ER Level and Response to Endocrine Therapy*

ER LEVEL (FMOL PER MG PROTEIN)	PER CENT RESPONSE
0 to 3	6
4 to 100	46
101 to 1000	81

Table 3. *ER and PgR in Metastatic Tumor Tissue*

RECEPTORS	PER CENT
ER−PgR−	33
ER−PgR+	1
ER+PgR−	27
ER+PgR+	39

low ER responded to endocrine therapy, whereas 46 per cent of tumors with an intermediate ER concentration and 81 per cent with a high level regressed. Several other laboratories have now confirmed these results. Thus, quantitating ER in a breast cancer specimen further enhances our ability to select patients for endocrine therapy.

Progesterone Receptor

In normal target tissues such as the uterus, a biological effect induced by progesterone requires priming of the tissue by estrogen. This observation is explained by the fact that estrogen induces the synthesis of progesterone receptor (PgR). Since PgR is an end product of estrogen action, the measurement of PgR in breast tumor specimens has been proposed as a method of determining the presence of an intact estrogen response pathway, thereby providing a better marker of the hormone dependence of a tumor.[10] Recently several laboratories have been measuring ER and PgR in breast tumors and correlating the results with response to hormone therapy. In our laboratory ER and PgR assays in more than 100 metastatic tumor specimens (Table 3) show that about a third of tumors have neither receptor, a third have only ER, and a third have both receptors. PgR was rarely found in ER negative (hormone independent) tumors, supporting the original hypothesis that estrogen regulates PgR synthesis in breast cancer tissue. By the above hypothesis the group of tumors containing ER and PgR should have the highest response rate to hormone therapy. The data in Table 4 pooled from three studies are preliminary but clearly show an increased remission rate in tumors containing both receptors (79 per cent).[1, 10, 14] Only one patient with neither receptor had an objective response to hormone therapy. ER negative, PgR positive tumors were too

Table 4. *Objective Remission of Metastatic Breast Cancer as a Function of ER and PgR*

RECEPTORS	TOTAL PATIENTS	NO. OF REMISSIONS (%)
ER−PgR−	20	1 (5)
ER+PgR−	31	8 (26)
ER+PgR+	47	37 (79)

Table 5. *PgR as a Function of ER Level in Metastatic Tumors*

ER level (fmol per mg protein)	per cent PgR positive
0 to 3	5
4 to 100	43
101 to 1000	82

infrequent for valid clinical correlations. ER positive, PgR negative tumors had an intermittent regression rate (26 per cent). If the above hypothesis is correct, one might ask why certain PgR negative tumors respond to treatment since the absence of PgR should indicate hormone independence. One could speculate that the responders in this group had a false negative PgR assay because of insufficient endogenous estrogen to stimulate PgR synthesis and not because of a defect in the estrogen response mechanism. Perhaps short-term estrogen administration to patients (particularly postmenopausal) to stimulate PgR synthesis prior to tissue biopsy might identify this group of patients. Alternatively, in premenopausal patients, high circulating progesterone levels at certain times in the menstrual cycle might occupy and mask receptor sites, also resulting in a false negative PgR assay. Additional data are needed in this regard.

Thus, quantitating the absolute level of ER and measuring PgR both enhance the clinician's ability to select patients for endocrine therapy. It is not clear, however, if measurement of PgR provides additional information beyond that given by the correlation between absolute ER level and tumor response. Since tumors with high levels of ER are more likely to contain PgR (Table 5), these assays may actually be identifying the same group of patients. In fact, in our series 82 per cent of tumors containing more than 100 fmol per mg protein ER (a group with an 80 per cent response rate to endocrine therapy) also contain PgR. Further study will be necessary to define the exact role of each of these assays in our management of patients with breast cancer.

Nuclear Estrogen Receptor

Several plausible explanations may be advanced to account for the fact that about one-third of ER positive tumors do not respond to hormone manipulations and are hormone independent despite the presence of receptor. Based on the schema of steroid hormone action (Fig. 1), hormone independence could be due to an absent or abnormal receptor, a defect in translocation to the nucleus, or defective nuclear events. Measurement of PgR (an end product of estrogen action) is an attempt to ascertain the functional integrity of the estrogen response pathway. An alternative approach, measurement of nuclear estrogen receptor, has been proposed as a method of determining that cytoplasmic receptor binding and nuclear translocation are functional.

Recently our laboratory has developed assays for nuclear estrogen

receptor in human breast tumors.[10] The results are too preliminary for clinical correlations, but a few observations have been made. First, certain tumors contain cytoplasmic ER but no nuclear ER, suggesting that these tumors might be hormone independent by virtue of defective nuclear translocation of receptor-hormone complexes. Second, other tumors contain both cytoplasmic and nuclear ER, suggesting an intact mechanism of action. Finally, certain tumors contain nuclear estrogen receptor that is not bound to estrogen ("free" nuclear receptor), a phenomenon not observed in normal target tissue. The significance of this finding is not known, but it is tempting to hypothesize that cytoplasmic ER in certain malignant cells might be capable of translocating to the nucleus and promoting growth and other estrogenic effects even in the absence of estrogen. Such tumors would not respond to ablative or additive estrogen therapy despite a positive ER or PgR assay since the biologically active free nuclear receptor would function regardless of changes in the hormonal milieu. However, antiestrogen therapy might be a plausible alternative in such patients, since antiestrogens could theoretically bind to and deactivate free receptors, resulting in tumor regression. These preliminary findings need further study.

ANTIESTROGEN THERAPY OF METASTATIC BREAST CANCER

Antiestrogens are compounds that antagonize the effects of estrogen when given at certain concentrations and schedules; under other conditions they may actually be estrogenic. The mechanism of action of antiestrogens is not clearly defined. However, a probable mechanism involves antiestrogen interaction with cytoplasmic and/or nuclear estrogen receptor (see above). In any event, the effectiveness of antiestrogens has now been proved by extensive clinical trials in women with metastatic breast cancer. They are active in both premenopausal and postmenopausal patients, although most studies have focused on the latter group. In postmenopausal patients not selected on the basis of tumor ER, the response rates to antiestrogen are similar to that for high dose estrogens (30 to 40 per cent), with a low incidence of significant toxicity. Just as with other endocrine therapies, the ER assay is useful in selecting patients likely to respond to antiestrogen therapy. Response rates from pooled data previously reviewed from several laboratories for the two most studied antiestrogens are shown in Table 6.[10] Nafoxidine has certain toxic side effects and is not available for general use in this country. Tamoxifen recently became available for general use. Although the optimal dose of this nonsteroidal antiestrogen has not been rigorously determined, there is a suggestion that tamoxifen may be more effective at low doses (approximately 10 mg per m^2 twice daily). Because of tamoxifen's relatively high response rate and therapeutic ratio, in our opinion it may be the endocrine treatment of choice for postmenopausal women. The use of tamoxifen as adjuvant therapy following surgical resection of primary hormone dependent tumors needs investigation.

Table 6. *Response Rate of Human Breast Cancer to Antiestrogens**

ANTIESTROGEN	NO. OF PATIENTS	RESPONSE (%)
Nafoxidine	94	34 (36)
Tamoxifen	389	148 (38)

*Adapted from reference 10.

THE USE OF ER AS A PROGNOSTIC FACTOR

Further analysis of the ER data in patients undergoing curative surgery for primary breast cancer has led to another important use for the ER assay.[6, 7] In 190 patients with surgically treated primary breast cancer, patients with ER negative tumors had recurrences at a significantly faster rate than those with ER positive tumors (Table 7). Twenty months after mastectomy, 36 per cent of all patients with ER negative tumors had recurrent disease, compared with only 17 per cent in the ER positive group. A similar pattern was observed even when the patients were categorized by their axillary node status. In both axillary node negative (Stage I) and positive (Stage II) patients, the recurrence rate was significantly greater for ER negative tumors. Further analysis showed that regardless of patient's age or menopausal status, size or location of the tumor, or the administration of postoperative radiotherapy, the disease free interval was shorter in patients with ER negative primary tumors. Thus, the ER status of a primary breast tumor is an important prognostic marker for rate of recurrence, independent of other known prognostic variables. This observation has now been confirmed by several other investigators. These data suggest that ER negative tumors have a more rapid proliferative capacity, supporting previous observations that such tumors have a relatively high thymidine labeling index, indicating a more rapid rate of DNA synthesis.[11]

These observations have important clinical implications. First, because of the prognostic importance of ER, all future adjuvant treatment studies in primary breast cancer should include this variable in stratifying patients. Second, the ER status of a primary tumor may

Table 7. *Recurrence Rates According to ER Status*

PATIENTS	NO. OF PATIENTS	RECURRENCE AT 20 MONTHS (%)	
		ER+ (%)	ER− (%)
All	190	19/113 (17)	28/77 (36)
Node−	91	4/54 (7)	8/37 (22)
Node+	99	15/59 (25)	20/40 (50)

help in planning new adjuvant treatment strategies not only by selecting patients for adjuvant hormonal therapy, but also by selecting subsets of patients with high recurrence rates who may benefit from more aggressive management.

USE OF RECEPTOR ASSAYS IN TREATMENT PLANNING

From the data discussed above, we have formulated a possible approach to the treatment of primary and metastatic breast cancer. A schematic outline for the adjuvant therapy of primary breast cancer is shown in Figure 2. After mastectomy or other local management, patients can be grouped according to their axillary node and tumor ER status into four groups with different risks for recurrence of tumor. Patients with ER positive tumors and negative axillary nodes (Stage 1) have the least aggressive disease and lowest recurrence rate. Perhaps these patients should be followed without treatment. Alternatively, endocrine therapy might salvage the relatively small percentage of patients in this group who already have micrometastases at diagnosis. Receptor positive patients with positive nodes have a worse prognosis and should be considered for adjuvant endocrine therapy. Previous studies reporting no survival benefit with adjuvant endocrine therapy need to be repeated with the addition of the ER assay to select appropriate patients. Chemotherapy might also be considered in this group of patients since not all ER positive tumors are hormone dependent, and since the tumor may include receptor negative cells. Those patients with ER negative tumors are not likely to benefit from hormonal management. Adjuvant chemotherapy (at least in premenopausal patients) should be used in view of the aggressive behavior of these tumors and high recurrence rates even when initially confined to the breast (Stage 1). It will be interesting to see whether adjuvant chemotherapy also benefits subgroups of postmenopausal women stratified by their ER status.

Therapy for patients with previously untreated metastatic breast cancer should be directed by the hormone receptor status of the tumor

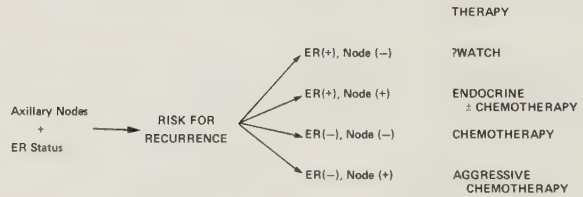

Figure 2. Adjuvant treatment strategy according to estrogen receptor protein (ER) and axillary node status.

and the clinical setting. It should be emphasized that additional tumor tissue should be obtained, if possible, for receptor assay at the time of recurrence or when changing therapy, since the tumor receptor status may change. Chemotherapy is appropriate for patients with ER and PgR negative tumors, which are not likely to respond to endocrine therapy. Patients having tumors with positive ER but negative PgR present a dilemma, since about 30 per cent respond to endocrine therapy. Endocrine therapy might be given to those patients in this group without extensive visceral metastases, whereas chemotherapy might be reserved for treatment failures and patients with advanced life-threatening visceral disease for which a rapid response is mandatory. Combined chemo-endocrine therapy also neeeds evaluation in this setting. Finally, endocrine therapy should be considered for all patients with positive ER and PgR assays, or in those with high levels of ER. In the few patients in this group with extensive life-threatening visceral metastases a combined treatment regimen is warranted.

These treatment approaches are tentative and represent only guidelines for a more rational approach to the management of breast cancer. They include hypotheses to be tested by future clinical trials, and should not be interpreted as the only method of treatment. It is certain, however, that basic research into the mechanisms of hormone action in breast cancer has dramatically altered the clinical approach to this disease. Further basic research may unravel still more of the enigmas of hormone dependent breast cancer, and may provide valuable clues to our understanding of the neoplastic process itself.

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The Current Status of Adjuvant Chemotherapy

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FUNDAMENTAL CONSIDERATIONS

Most patients with carcinoma of the breast do not have detectable distant metastases at the time of first presentation. Nevertheless, approximately half of those with operable tumors develop recurrent disease. At the present time, the best predictor of prognosis after mastectomy is the degree of involvement of lymph nodes in the ipsilateral axilla.[10] When there is no such involvement, the recurrence rate at 5 years is 21 per cent and survival 76 per cent, but, if demonstrable axillary node metastases are present at the time of mastectomy, the recurrence rate rises to 66 per cent, and survival drops to 54 per cent. In the presence of extensive axillary disease, namely when four or more nodes are found to contain tumor, the recurrence rate at 5 years is 81 per cent, and survival at that time 31 per cent.

The reason for the frequent failure of local therapy to eradicate ostensibly localized disease is because undetectable metastases are present at the time of primary diagnosis. This suggests that if the prognosis of operable breast cancer is to be improved, systemic cytotoxic chemotherapy may be needed as part of the primary management. Less sensitive to chemotherapy than the leukaemias and lymphomas, carcinoma of the breast is the one common malignant tumor that is frequently responsive to cytotoxic chemotherapy. The more active cytotoxic drugs include alkalating agents, methotrexate, 5-fluorouracil, vinca-alkaloids, and Adriamycin.[3]

Experimental data suggest that neoplastic cell populations proliferate with characteristics that can be expressed mathematically by a Gompertz equation, which means that growth is at every instance exponential, but with a growth constant that is simultaneously decreas-

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ing exponentially.[16] This implies that as a tumor increases in size, so the number of cells within it which are actively participating in cell division are decreasing. In other words, as the tumor ages its growth fraction diminishes. Because cytotoxic drugs are dependent upon cell proliferative activity for their action, the above considerations indicate that chemotherapy is more likely to eradicate small, rather than large, cell populations. Thus, if the aim with chemotherapy is cure, not just palliation of advanced disease, chemotherapy should be used as part of the primary treatment of cancers known to have a high probability of recurrence. This approach has become known as "adjuvant chemotherapy," and has been successful in the treatment of certain tumors in childhood, particularly Wilms' tumor.[4]

ADJUVANT CHEMOTHERAPY FOR OPERABLE BREAST CANCER

Early trials of adjuvant chemotherapy in operable breast cancer were based on the concept that cells, disseminated from the primary tumor into the circulation at the time of surgery, were responsible for the development of distant metastases. One of these trials compared triethylenethiophosphoramide (Thiotepa; TSPA) given at the time of operation and for two days postoperatively with no adjuvant treatment.[8] The administration of TSPA led to a reduction in the recurrence rate and improved survival in premenopausal patients with four or more involved axillary nodes.[11] Another trial showed an improved survival following the use of a short course of cyclophosphamide postoperatively.[13]

In more recent trials, it has been assumed that occult dissemination has already occurred in many patients by the time of diagnosis and before treatment. Furthermore, adjuvant systemic therapy has been planned on the assumption that the cytotoxic drugs act by first order kinetics. This means that, in response to a single dose of a cytotoxic agent, a certain proportion, rather than a fixed number, of tumor cells are killed. Consequently, chemotherapy is given intermittently and for prolonged periods, in order to allow bone marrow recovery between courses.

In 1972, a trial was started jointly by the National Surgical Adjuvant Breast Project (NSABP), the Eastern Cooperative Oncology Group, and the Central Oncology Group. Women with involved axillary lymph nodes after radical or modified radical mastectomy were randomized to receive either a placebo or L-phenylalanine mustard (L-Pam) orally for 5 days every six weeks for two years postoperatively. The preliminary results of this trial showed that treatment failures occurred in 22 per cent of 108 patients receiving the placebo and 9.7 per cent of 103 women given L-Pam ($P=0.01$). In premenopausal women, treatment failure occurred in 30 per cent of those receiving placebo, and 3 per cent of those treated with L-Pam ($P=0.008$). A similar trend was observed in postmenopausal patients but the difference was not

statistically significant.[6] This trial engendered worldwide interest. Being a relatively ineffective drug in the advanced disease, the results with L-Pam were unexpectedly good. Furthermore, because it does not cause severe subjective toxicity and is easily administered, it has considerable appeal for use in ostensibly disease-free patients. The results have been reaffirmed in a subsequent report and it has been suggested that they may be improved further by the addition of 5-fluorouracil (FU) to L-Pam.[7] Current NSABP trials are comparing L-Pam + FU vs. L-Pam + FU + methotrexate, L-Pam + FU vs. L-Pam + FU + tamoxifen, and L-Pam + FU vs. L-Pam + FU + *Corynebacterium parvum*.[9]

In 1973, another randomized controlled trial was established to study the effect of prolonged combination chemotherapy with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). The treatment was given to those patients with histologically involved axillary nodes who had undergone radical mastectomy.[1] A recent analysis of this trial of 207 patients has shown a relapse rate of 45.7 per cent in control patients compared with 26.3 per cent in women given CMF ($P<0.0001$). There is no difference in the recurrence rate for postmenopausal women, and the statistically significant benefit from CMF is seen only in premenopausal patients. Although 21.4 per cent of control patients have died compared with 10.4 per cent of those treated with CMF, this difference is not significant.[2]

The results so far available have shown that adjuvant chemotherapy causes a prolongation of the postoperative disease-free interval in premenopausal patients only. This suggests that the effect may be mediated by suppressing ovarian function. The preliminary results with adjuvant CMF have tended to be better in premenopausal patients when amenorrhea has been induced.[2] Furthermore, the incidence of amenorrhea in patients receiving L-Pam is higher than in control patients,[15] indicating that this drug too may suppress ovarian function. Moreover, it has now been demonstrated that prophylactic ovarian irradiation combined with prednisone results in an improvement in both the recurrence-free interval and survival in premenopausal women after mastectomy.[12]

ADJUVANT CHEMOTHERAPY FOR LOCALLY ADVANCED INOPERABLE BREAST CANCER

Locally advanced, primarily inoperable breast cancer (Stage III) is treated usually by radiotherapy, which may be combined with palliative surgery. Survival after local treatment is poor, and most patients develop distant metastases.[14] Hence, combining chemotherapy with local treatment can also be considered in the primary management of this stage of the disease. In a recent trial,[5] 110 patients with primary inoperable breast cancer were treated by chemotherapy before radiotherapy with the intention of suppressing subclinical distant metastatic disease. The patients achieving a complete regression of the local disease were then allocated at random to receive either no further

treatment or six more cycles of adjuvant chemotherapy. It was found that the recurrence-free interval was prolonged significantly by maintenance chemotherapy, but this benefit applied only to local recurrence, whereas the incidence of distant metastases and survival remained the same. It was also noted that the combination of chemotherapy and radiotherapy in the initial treatment of patients in this series led to an improved survival compared with the results in an earlier study using local therapy alone. However, this retrospective comparison is of doubtful validity, particularly in this instance when a higher irradiation dose was used in the latter study. The optimal combination of local and systemic treatment for Stage III breast cancer will not be known until long-term trials have evaluated the many options available.

PROSPECTUS

At the present time, trials have shown that prolonged adjuvant chemotherapy leads to a lengthening of the postoperative disease-free interval in premenopausal patients only. There has been no significant benefit to postmenopausal women, and the trials are of insufficient duration to give valid information on survival. There are potential hazards with prolonged cytotoxic chemotherapy, such as the induction of second malignancies.[17] While such hazards may be of little relevance to the patient with heavy axillary node involvement, and hence with a grave prognosis, they are of particular concern to those patients who may have been cured by local therapy alone. Clearly, in the present state of our knowledge, adjuvant chemotherapy should be administered only in controlled clinical trials designed to assess its contribution. Historical controls should not be used because observer bias and selection of cases may invalidate the conclusions drawn. Indeed, it is conceivable that even the natural history of disease may change with time.

At present, only patients with a high risk of developing recurrent disease should be selected for trials of adjuvant chemotherapy. Risk status is assessed from a knowledge of axillary node involvement, although attempts are being made to discover other markers of prognosis. The development of such markers would also assist in the monitoring of tumor load at subclinical levels, so that schedules of systemic therapy could be planned more accurately.

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Ovarian Suppression and Breast Cancer

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In 1889 Schinzinger[24] suggested that castration by oophorectomy might be effective treatment for some women with advanced breast cancer. Seven years later in 1896, Sir George Beatson[2] of Glasgow performed oophorectomy in three women, two with recurrent and one with an advanced primary breast cancer. These operations culminated years of experimental investigations into ovarian function and lactation, and his logical thought processes represent sound clinical application of basic laboratory research.

In 1978, issues about the value and timing of castration (prophylactic or therapeutic), the method used to achieve it (surgery or radiation), and the use of combined adjuvant treatment plus castration (steroids and/or chemotherapy) remain unresolved.

Evaluation of studies that address some of these issues is historical because estrophile protein determinations were not available at the time of many reports. Thus an overall response rate following oophorectomy of 20 to 40 per cent may be overstated or understated depending on the unknown factor, the levels of estrogen receptor in these series.[3, 7, 9, 12, 13] The importance of these determinations as predictors of response is emphasized in the article by Osborne and McGuire in this symposium. Estrogen receptor determinations may predict who will respond to castration, but they do not resolve the issue of timing, method, and adjuvant treatment. These will be discussed in this chapter.

Timing of Castration: Prophylactic Versus Therapeutic

The systemic nature of breast cancer and occult metastases has already been discussed in previous articles. It would seem reasonable

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to offer castration to women with "favorable" breast tumors when metastases are not evident, with the hope of prolonging survival and the tumor-free interval from the time of mastectomy.

An attempt to determine the role of "early" and "prophylactic" castration has been made in at least five well designed studies. In 1934 Taylor[23] compared early castration in 47 women with therapeutic radiation castration in 50 women. All had radical mastectomy. There was no benefit to early castration either in terms of survival or delayed recurrence.

The National Surgical Adjuvant Breast Project (NSABP) studied premenopausal women under age 50 who at the time of radical mastectomy were randomized to oophorectomy or a control group.[22] Unfortunately, triethylenethiophosphoramide (Thiotepa) was administered to many women, a factor which may have altered the control group. The follow-up period was limited to 36 months in most women, although some were followed 5 years. There was no difference in survival or time to recurrence from mastectomy. The status of axillary nodes did not affect results.

The results of a trial from Manchester, England between 1948 and 1955 were recently published.[5] Two hundred ninety-three patients who underwent radiation castration and 345 control patients were followed for at least 15 years. The crude survival at 15 years for patients with negative or positive axillary nodes was similar in radiated and control patients. One significant difference was fewer distant metastases in the radiated groups when compared with the control group (58 versus 49 per cent, $P < 0.05$). There was a trend (not statistically significant) to fewer local recurrences (26 versus 31 per cent) in castrated patients and a delay in the recurrence of the tumor after castration, but again this fell short of statistical significance. A criticism of this study was that menses returned in 19 of 58 women younger than 40 years, although return of menses was not correlated with recurrent tumor. There was a longer tumor-free interval from surgery to recurrence after radiation. Although the differences were not significant, 21 per cent of control patients had recurrences or died within 3 years compared with an identical incidence of recurrence or death in the treated group at 7 years. Some of these differences were significant at 5 and 10 years.

An important long-term study, begun in 1951 by Nissen-Meyer,[18, 19] was recently reviewed. Again patients were randomized into radiated and control groups. At 15 years the tumor-free survival was significantly better in the irradiated group than in the control group ($P < 0.05$), although crude survival was the same in both groups. At 15 years, 22 control patients had recurrence versus 9 in the castrated group. Tumor-free intervals averaged 5.58 years longer in radiated patients.

Other studies, particularly one by Kennedy, Mielke, and Fortuny,[12] represent detailed and methodical analyses of retrospective data. They reviewed studies and trials from 1889 to 1964, and then compared 119 women treated with immediate castration and 177 women treated

with late or prophylactic castration. Both radiation and surgery were employed and hormonal therapy and chemotherapy were also utilized. They noted a longer tumor-free period from surgery to recurrence after early castration with no difference in survival. Within the limits of retrospective reviews, these conclusions support the findings in two of the three prospective studies.

Therapeutic Castration

The role of therapeutic castration by either surgery or radiation has also engendered much discussion. Much of the discussion about patient selection with recurrent disease is historical, since estrogen receptors will predict (with up to 85 per cent accuracy) a response to castration. Regression rate in estrogen receptor negative patients is uncommon and castration generally should be avoided. In a report by Block, Jensen, and Pooley,[3] none of 42 estrogen receptor negative patients responded to hormonal treatment or castration. Similar statistics are reported by Osborne and McGuire elsewhere in this symposium.

Even before estrogen receptor determinations were available, good but less accurate means were used to predict response to castration. Puga, Welch, and Bisel[21] reviewed 145 cases of oophorectomy between 1960 and 1964. All patients were either menstruating or within one year of menopause. Seventy-five (52 per cent) had objective remission and 70 (48 per cent) failed to improve. The average duration of remission was 17 months (range 1 to 72 months). The mean survival for responders after castration was 3 years as compared with 1 year in nonresponders. A good response was correlated with small tumor masses and metastases to bone, lymph nodes, or lung. Although an occasional spectacular long-term remission of visceral metastases follows castration, this did not occur in this series. The patient's age, histologic type of breast cancer, and length of disease-free interval could not be correlated with response to castration. A less accurate test used before estrogen receptors to predict response to castration has been suggested by Minton.[26] Levodopa, a drug that decreases prolactin levels, may cause a decrease in cellular metabolism of breast cancer cells. When given to women with osseous diseases, relief of pain follows immediately and these patients frequently respond to endocrine ablation.

Techniques of Castration

Two methods of castration are oophorectomy and radiation. Each method has its proponents. The advantages of surgical castration are an immediate effect, and the opportunity to explore the abdomen in order to exclude liver or other visceral metastases. Finally, surgery ensures complete removal of ovarian tissue and the chance for histologic examination (metastases to ovary are not infrequent). Those who favor radiation castration cite the avoidance of a second operation and of possible immunosuppression in compromised hosts. Most important is the equal success of surgery and radiation.

Few studies have attempted to compare radiation and surgery.

Nissen-Meyer[20] performed a controlled study and found a better crude survival from 5 to 15 years after radiation castration, although this difference was not statistically significant. The calculated x-ray dose was 1000 rads to the ovaries given over 6 weeks.

In the Manchester study there was a return in menstrual function in one-third of the women younger than 40 years of age. Although these "failures" were not necessarily followed by recurrent tumor, it may explain why some oppose radiation castration.

Both methods are effective. The choice must be individualized and should take into account patient convenience.

Castration by Use of Steroids

Since the adrenal cortex produces cortisol, androgens, and estrogens, suppression of these by exogenous steroids (20 to 30 mg per day) may potentiate the effects of castration. Exogenous prednisone, by inhibiting the formation of ACTH, would also hopefully suppress androgens and estrogens. Although randomized trials are not available and experience is limited, the "impression" in one large study was that this additional treatment did increase the percentage and duration of remissions.[18, 19] Urinary studies have shown a decrease in excretion of metabolites of these hormones as well. Castration plus adrenalectomy has been practiced by some groups and is discussed elsewhere. The absence of controls and frequent addition of other treatment make all of these data difficult to analyze.

Castration Plus Chemotherapy

Since castration may be followed by tumor regression in 20 to 70 per cent of cases and combined chemotherapy is followed by a response in up to 70 per cent of cases, it has been suggested that a combination of castration and chemotherapy would be better than either alone. In a recent study, 75 patients with recurrent or advanced breast cancer were randomized into three groups: control; castration plus immediate chemotherapy; or castration plus chemotherapy when recurrence was noted.[1] The total numbers in each subgroup were small, estrogen receptors were not studied, and the choice of chemotherapeutic agents questioned, but objective responses were greater in those receiving adjuvant therapy. When patients showed early progression of tumor, none of these treatments was effective. After oophorectomy the median time of tumor regression was 33 weeks; it was 72 weeks after oophorectomy plus adjuvant chemotherapy ($P < 0.05$).

Castration and Breast Disease

An additional theoretical benefit of oophorectomy is to decrease proliferation of acinar breast tissue by withdrawal of estogen stimulation. If estrogen stimulation is a factor in breast cancer, then the incidence of new cancers should be less after castration. The relationship between estrogens and breast cancer is difficult to prove, individual cases notwithstanding.

Hoover et al.[10] followed 1891 women given conjugated estrogens

for 12 years after menopause. Thirty-nine breast cancers were anticipated and 49 diagnosed. The development of neoplasms was not strictly dose related, but a greater risk was noted in women using high doses for more than 10 years. An especially high risk was noted in postmenopausal women in whom benign breast disease developed after estrogen therapy was started.

Burch, Byrd, and Vaughn[4] studied 735 women followed for an average of 15 years after estrogen therapy was started. Half of the group had undergone oophorectomy, but the anticipated protection against breast cancer was not noted after estrogen therapy was begun.

These studies have shown that estrogens taken postmenopausally do not protect against breast cancer. Estrogens have not been proved to be a cause of breast cancer. If estrogen stimulation of breast tissue must be chronic to cause neoplasia, then the postmenopausal patients are not the group to study. Feinleib[8] reported on 1278 women with artifical menopause following hysterectomy and oophorectomy before age 40. The patients were followed 20 to 40 years and only 6 developed breast cancer as compared with an expected incidence of 24. Previous pelvic irradiation was also protective, although the relationship to age is unclear. Hysterectomy and bilateral oophorectomy done before age 40 reduced the risk of developing breast cancer later in life by approximately 75 per cent. For this reason, in some young women treated by partial mastectomy or in those who have a strong family history of cancer, radiation should be considered.

Summary

Castration by radiation or oophorectomy may cause regression of tumor metastasis.

Patients who will benefit are those whose estrophile protein concentration in breast tissue is high.

The use of castration as an early adjunctive method (prophylactic castration) delays the onset of recurrence, although it may take 10 to 15 years to verify these observations. Difficulty in analyzing these data is due to the smallness of the sample, and the frequent use of hormones in control patients.

Effective castration may be observed with radiation or surgery. The choice is dependent on the patient's wishes and the need for an immediate effect.

Combination therapy with steroids, chemotherapy, or adrenalectomy may potentiate the effect of castration.

Premenopausal castration may markedly decrease the incidence of new breast cancers, particularly when followed for 20 or more years.

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The Value of Adrenalectomy in Patients with Metastatic Breast Cancer

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Theoretical and Historical Considerations

Although excision of endocrine glands for the treatment of metastatic breast cancer was introduced as early as 1896 by Sir George Beatson, it was based on empirical observations in the absence of any concept of endocrinology. The operation soon fell into disfavor and by 1905 was no longer practiced.[1] The concept of "hormone dependence" is derived from the classic experiments of Huggins in his study of the metabolic effects of hormones on the prostate in the dog.[10] It was this laboratory finding that led Huggins to perform orchiectomy for metastatic cancer of the prostate.[12]

The adrenal cortex in humans secretes glucocorticoid, mineralocorticoid, and sex steroid hormones. Although there has been no evidence that the human adrenal cortex secretes estrogens, it is now well established that an adrenal androgen, androstenedione, is peripherally converted to estrogens.[17] It has been demonstrated that women with breast cancer after menopause or oophorectomy still excreted significant and even large amounts of estrogenic hormones in the urine; these hormones were further reduced or became unmeasurable after adrenalectomy.[2] In experimental animals the adrenal cortex is known to be involved as an etiologic factor in the genesis of mammary tumors in certain strains of mice.[16] When the gonads in these mice were removed at an early age, estrogen-secreting adrenal tumors occurred.[8]

Bilateral total adrenalectomy for the treatment of human cancer was first performed in 1945,[11] but hormonal maintenance was not satisfactory because 11-oxygenated corticosteroid was not available for replacement therapy. When cortisone became available in abundance

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in 1951, bilateral adrenalectomy could be safely performed without the fear of adrenal crisis occurring during surgery. Patients having undergone adrenalectomy could now live a normal life on hormonal replacement therapy.

Preoperative and Postoperative Hormonal Substitution Program

The human adrenal gland, particularly the adrenal cortex, is indispensable to life. It secretes a number of hormones that are intimately concerned with electrolyte and fluid metabolism, carbohydrate and protein metabolism, and the response of the organism to stress. The purpose of adequate hormonal replacement therapy is to provide adrenal hormones in such concentrations that adrenal insufficiency does not develop during surgery or in the postoperative period. The substitution program initially developed in 1951[9] has been proved effective, and we have performed many hundreds of adrenalectomies without the development of postoperative adrenal insufficiency. Our increased clinical experience in the management of "adrenal-less" patients, however, has enabled us to modify hormonal substitution therapy to a very simple schedule that has been used routinely on our service for the last 10 years. The major difference between the new schedule and the one that has been widely used since 1951 is the elimination of preoperative administration of large doses of cortisone and desoxycorticosterone (DCA). The first dose of cortisone acetate (150 mg) is given intramuscularly immediately after the right adrenal gland is excised. Simultaneously, cortisol (100 mg) is given by slow intravenous infusion over 3 to 4 hours. The second dose of cortisone acetate (100 mg) is given intramuscularly after the removal of the left adrenal gland, and, therafter, cortisone acetate (50 mg) is given intramusculary every 4 hours. On postoperative day 1, cortisone acetate is reduced to 50 mg intramuscularly three times daily, and then 50 mg intramuscularly twice daily on postoperative day 2. On postoperative day 3, the cortisone acetate can be given orally in doses of 25 mg three times daily, and by day 4 the maintenance dose of cortisone, (25 mg orally twice daily), is reached and continued.

Our criterion for adequate replacement therapy is freedom from all signs and symptoms of adrenal insufficiency, including normal salt, carbohydrate, and blood pressure balance. This can be accomplished in at least 90 per cent of cases by oral administration of cortisone acetate or hydrocortisone. The patients are well able to withstand the everyday stresses of living and have a sense of well being. In the rare event that a patient should develop postural hypotension with accompanying symptoms, the use of a long-acting mineralocorticoid, desoxycorticosterone-trimethylacetate or pivolate (25 mg) intramuscularly once a month will correct the postural hypotension.

Patients with advanced metastic cancer who are to undergo adrenalectomy are often in a poor state of nutrition, and an attempt should be made to correct the lowered blood volume and plasma proteins by transfusions. Careful evaluation should be made of the renal, pulmonary, and cardiac status of the patient, for it is in these systems that postoperative complications are seen.

Indications and Contraindications for Adrenalectomy

Bilateral adrenalectomy is indicated in the following patients: (1) those with metastatic cancer of the breast, particularly those who are postmenopausal; (2) those with inflammatory carcinoma of the breast, combined with oophorectomy in premenopausal women;[5] and (3) postmenopausal women with "high-risk" breast cancer following mastectomy (those with four or more axillary lymph nodes containing metastases) as adjuvant therapy.[6]

Adrenalectomy is contraindicated in: (1) patients having medical evidence of cardiovascular or renal diseases; (2) patients with extensive liver metastases, demonstrating signs and symptoms of hepatic failure (liver metastasis per se is not a contraindication); (3) patients with extensive pulmonary metastases, having signs of pulmonary insufficiency that may complicate general anesthesia; (4) patients with brain metastases having had seizures (brain metastasis per se is not a contraindication); (5) patients with gastric or duodenal ulcer that may be aggravated by corticosteroids; (6) patients with cancer of other sites; and (7) patients who are 75 (or over) years of age.

Clinical Investigation

The beneficial effects of bilateral adrenalectomy for women with metastatic breast cancer have been conclusively demonstrated. Clinical remission rates, based on objective criteria, have been reported to range from 39 to 67 per cent in several large series.[3] Therapeutic effects of adrenalectomy have been demonstrated in patients with metastatic lesions in different sites. The tumor regression observed objectively is always accompanied by subjective evidence of rapid relief of disabling symptoms. For example, women with crippling bone pain, often bedridden as a result of extensive osseous metastases, become ambulatory and free of severe pain soon after both adrenal glands are removed. The subjective symptomatic relief is often followed by roentgenologic evidence of healing pathologic fractures and recalcification of osteolytic metastases. The return of a bedridden patient to normal physical activity is most gratifying.

Marked respiratory symptoms in women with extensive pulmonary metastases often subside rapidly after adrenalectomy. This subjective relief of symptoms is invariably followed by objective evidence of tumor regression as demonstrated by chest x-ray film. Although many surgeons have considered liver metastasis to be a contraindication for adrenalectomy, we observed objective regression of hepatic metastases, as demonstrated by a decrease in size on palpation or liver scan, and marked reduction of enzyme levels such as alkaline phosphatase and SGOT, if the metastatic tumors were hormone-dependent, i.e., estrogen receptors were present. We, however, do not perform adrenalectomy in those patients who have clinical or laboratory evidence of hepatic failure. Similarly, we do not consider brain metastasis to be a contraindication for adrenalectomy, if the patient has had no clinical manifestation of seizures. We have observed objective evidence of tumor regression in women with cerebral metastases, even in cases

with signs and symptoms of impending hemiplegia. In successful cases these patients were able to experience complete restoration of motor function lasting many months. We do not advise adrenalectomy in patients with hemiplegia, especially in those who are hemiplegic for more than 48 hours.

Does primary adrenalectomy result in bettèr regression and survival rates than seconday adrenalectomy? A controlled, randomized trial to compare the therapeutic efficacy of primary adrenalectomy (surgery performed at the outset when metastases first become demonstrable) with secondary adrenalectomy (surgery performed after a trial of administering hormonal therapy) was carried out by the author and his coworkers several years ago.[7] The major conclusions that could be derived from this study were: the regression rate is higher in the primary adrenalectomy group (46 per cent) than in the secondary adrenalectomy group (30 per cent), but the overall survival time of the two groups of patients is very similar; the data disclose that there is a significant loss of patients, that is, patients died during or after hormonal therapy; some of them presumably would have been benefited by adrenalectomy if they had undergone the operation at the outset without a trial with hormonal therapy; the response or lack of response to hormonal therapy does not have any relationship to the subsequent response to adrenalectomy; and the data also disclose that while the castration responders do better after adrenalectomy, 23 per cent of castration failures will respond to subsequent adrenalectomy. The widely accepted assumption that castration failures will not respond to subsequent adrenalectomy is not supported by our data.

Theoretically, it may be advantageous to perform oophorectomy and adrenalectomy simultaneously to eradicate the major sources of steroid hormones, particularly the production of estrogens, in the treatment of premenopausal women with metastatic breast cancer. This approach, though conceptually logical, has not been carefully investigated. With the discovery in recent years of the concept of the estrogen receptor, clinical trials with simultaneous oophorectomy and adrenalectomy based on estrogen receptor data deserve serious consideration in the treatment of breast cancer.

The question of whether oophorectomy should accompany adrenalectomy in postmenopausal women with advanced breast cancer may be answered with some certainty, based on both clinical and scientific observations. Some surgeons routinely perform simultaneous oophorectomy and adrenalectomy in postmenopausal women, based on the premise that postmenopausal ovaries continue to produce estrogens. The validity of this assumption, however, is questionable for the following reasons: it is now well established that the source of estrogen in postmenopausal women is its derivation from adrenal androgens such as androstenedione which is peripherally metabolized into estrogens; the role of the ovaries in estrogen secretion in postmenopausal women is minimal; studies in a small series of patients in the author's laboratory show that oophorectomy failed to alter the low urinary levels of estrogens in patients who had previously undergone

adrenalectomy; and our clinical studies have not demonstrated a clear difference in the response rate, whether adrenalectomy was done alone or with simultaneous oophorectomy for the treatment of disseminated breast cancer in postmenopausal women. Dao and Huggins earlier reported a lack of evidence showing that simultaneous oophorectomy helped in women older than 54 years.[4] Presently we recommend simultaneous oophorectomy and adrenalectomy in postmenopausal patients only when their last menstrual cycle was within one year of the contemplated adrenal surgery.

Selection of Patients for Adrenalectomy

Bilateral adrenalectomy is an operation of some magnitude and induces regression of cancer in about half of the patients with disseminated breast cancer. Furthermore, the care of adrenalectomized patients can be complex at times, not to mention the psycho-economic effect of the surgery. Thus, if response to adrenalectomy could be predicted with reasonable accuracy, unnecessary major surgical procedures could be avoided for those who would not attain remission. Most clinical criteria used for the selection of patients for adrenalectomy, such as "disease-free" period, age, extent of metastases, response to previous hormonal therapy, are unreliable. Previous response to surgical castration is perhaps the only criterion that is of some use for predicting subsequent response to adrenalectomy. Our study revealed that at least 50 per cent of those responding to castration would be benefited again after adrenalectomy.[7]

Urinary and serum steroid levels in women with breast cancer have been measured by many investigators to predict clinical response to endocrine ablations, but the results have largely been disappointing.

In recent years, studies of intracellular macromolecules with high and stereospecific affinity for estrogens have revealed the existence of specific protein "receptors" in estrogen-sensitive tissues, such as those of the uterus, vagina, and anterior pituitary,[14] and, of particular interest, in mammary tumors from rats and human patients.[13] The cytoplasmic estrogen receptor protein (ERP) in human breast tumors can be measured by several methods. Earlier reports show that breast cancer that responded favorably to endocrine ablation contained quantities of specific estradiol receptors, whereas those tumors that did not possess high affinity for estrogen regularly failed to respond.[15]

In our series of 84 patients undergoing adrenalectomy for metastatic breast cancer, estradiol receptors (ER) in the metastatic tumors were measured before surgery. Results of this study are summarized in Table 1. The data disclose that of the 84 tumors examined, 56 (67 per cent) contained specific estradiol receptors of various species (4S, 8S, or 4S+8S), but ER was not measurable in only 28 (33 per cent) tumors. It appears that the number of positive tumors in our series is higher than earlier reports by others. One reason is that we consider 4S receptor species to be positive (they meet with the criteria as specific estradiol receptor proteins by sucrose density gradient analysis method). Results clearly show that patients with tumors that do not

Table 1. *ER in Human Breast Carcinoma and Response to Adrenalectomy*

ER	NO. OF PATIENTS	RESPONSE	FAILURE
Inactive	28	3	25
4S*	14	6	8
8S	9	5	4
4S+8S	33	22	11
TOTALS	84	36	48

Estradiol-receptor complex sediments at 4-5S (Svedberg's), or 8-9S on sucrose gradients. Human breast tumors may have 4S, 8S or both 4S and 8S.

contain any measurable ER are not likely to respond to adrenalectomy (only 3 patients or 11 per cent had objective remission). In contrast, about 60 per cent of the receptor-positive tumors regress after adrenalectomy. Our data and reports by others lead us to conclude that breast cancer that does not contain estrogen receptors rarely, if ever, responds to endocrine ablations; these patients should not be candidates for ablative procedures. It is also evident that not all receptor-positive tumors regress after adrenalectomy; only 60 per cent of those containing specific estrogen receptor will regress following endocrine ablative procedures.

Unfortunately, not all patients with metastatic cancers have lesions accessible for excision in order to perform estrogen receptor studies, particularly those patients with bone metastases. It is hoped that estrogen receptors in breast tumors can eventually be measured at the time of primary treatment so that the information can be used for future decisions on the indications for endocrine ablative therapy at the time that metastases appear.

The reasons for the lack of response in ER-positive tumors are not understood. There are several plausible explanations and further research is being directed toward elucidating this. While studies of other hormone receptors in the hormone-dependent breast tumor may be logically justifiable, technical problems pertaining to the specificity of hormone receptors remain. For example, the usefulness of measuring progesterone receptor has yet to be carefully examined.

Is Adjuvant Therapy with Adrenalectomy a Rational Approach?

About 10 years ago this author carried out a pilot study to examine the beneficial effect of adrenalectomy in postmenopausal women with "high-risk" breast cancer (those with four or more metastatic axillary lymph nodes) immediately after mastectomy. The study had two major objectives. Can we demonstrate a highly significant reduction in the mortality rate in a small series of high-risk breast cancer patients? Can adrenalectomized women live for a prolonged period with no "ill effects"? Our preliminary results from this small series following a six

year observation period were published.[6] The data disclose a statistically highly significant improvement in the 5 year survival rate among women who had adrenalectomy as adjuvant therapy after mastectomy. In addition, we observed a lack of ill effects among these adrenalectomized patients. We will be reporting the 10 year survival in this series. The results so far show that no patients have died in this series since our paper was published in 1975. This observation is extremely encouraging. The lack of a significant effect of cytoxic chemotherapeutic agents, used as adjuvant therapy in postmenopausal women with "high-risk" breast cancer, and the remarkable results from our pilot study of adjuvant adrenalectomy, make it imperative to examine the extended role of endocrine surgery as adjuvant therapy in "high-risk" patients. The discovery of the estrogen receptor concept in hormone-responsive breast cancer has provided us with a useful method for selecting patients for adjuvant adrenalectomy in postmenopausal women and adjuvant oophorectomy in premenopausal women with "high-risk" breast cancer.

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Hypophysectomy for Stage IV Breast Cancer

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More than 25 years have elapsed since hypophysectomy was first undertaken for the palliative treatment of patients with Stage IV breast cancer. The physiologic basis for this approach was the concept that pituitary hormones such as growth hormone and prolactin might play a role in stimulating the growth of breast cancer, and that elimination of these hormones from the circulation might induce tumor regression. Prior to undertaking hypophysectomy, it was known that ovariectomy could induce objective tumor regression in about 40 per cent of premenopausal women with metastatic breast cancer. This led to the concept that some breast cancers were estrogen "dependent." Also, bilateral adrenalectomy had been shown to induce remissions in women who had previously been castrated or in postmenopausal women. The adrenal glands were considered to be a secondary source of estrogens in the body. Thus, if pituitary hormones play a significant role in maintaining the growth of some human breast cancers, hypophysectomy should yield results superior to ovariectomy and adrenalectomy. On the basis of present evidence discussed below, estrogens appear to play the major role in maintaining the growth of hormone responsive breast cancer, perhaps by a direct action on the tumor. However, evidence will be presented which suggests that pituitary hormones may also play a role in some cases.

Techniques of Hypophysectomy

When hypophysectomy was first attempted it was found that total removal of the gland was more difficult than initially anticipated.[12] As

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Supported by grants from the United States Public Health Service (CA-05197-18, RR-80) and the American Cancer Society (PDT-48T).

a result, many techniques have been employed to obtain pituitary ablation including transfrontal craniotomy, transsphenoidal approaches, pituitary stalk section, stereotaxic cryosurgery and radiofrequency coagulation, interstitial irradiation, and external heavy particle radiation. Our experience has been primarily with the surgical procedures of transfrontal craniotomy,[11, 18] and in the past decade with transnasal, transsphenoidal microsurgical hypophysectomy,[1] which we have found to be most satisfactory in obtaining removal of the anterior pituitary that is as total possible. For successful results, it is necessary to have a neurosurgeon who is not only skillful but has a continuing experience with this painstaking technique.

With experience, operative morbidity and mortality have been reduced to minimal levels for both the transfrontal and transsphenoidal procedures. In the last 200 transsphenoidal hypophysectomies, surgical mortality has been less than 1 per cent and no major complications such as damage to vision, oculomotor nerves, or meningitis have been encountered.

Completeness of Hypophysectomy

For proper evaluation of the potential antitumor effects of hypophysectomy, it has been our opinion that total ablation of the anterior pituitary gland is essential. It is now relatively easy to determine the completeness of hypophysectomy, since radioimmunoassays for the measurement of all of the anterior pituitary hormones in serum are available. We routinely perform a thyrotropin releasing hormone (TRH) stimulation test on the fifth or sixth postoperative day prior to discharge. Five hundred μg of TRH are administered by intravenous push and multiple blood samples are obtained over a two hour period for the measurement of prolactin, thyrotropin, growth hormone, follicle stimulating hormone and luteinizing hormone. During the past two years with the use of this provocative test we have not encountered a single patient in whom any of the above five pituitary hormones were present in normal amounts. In the vast majority of patients all five hormones were undetectable in the serum, although in some, sporadic samples revealed low levels of hormone close to the sensitivity of the assay. In addition, we do not administer thyroid hormone replacement therapy until one or two months postoperatively when the serum thyroxin level has been demonstrated to be low. In the last 200 hypophysectomies 97 per cent of the patients showed suppression of thyroid function; in 3 per cent thyroid function was not suppressed, and in the majority of these, thyroid suppression tests revealed autonomous thyroid function and thus were not an indication of incomplete pituitary ablation. We have had occasion to restudy a number of patients months to years after hypophysectomy using various provocative tests and we have found undetectable levels of prolactin, growth hormone, FSH, and LH.

In our most recent series of transsphenoidal hypophysectomies, postmortem examinations were carried out in 23 patients in whom the sella turcica was removed en bloc and multiple sections were made.

Microscopic remnants of anterior pituitary tissue were found in six patients; two had only scattered pituitary cells, two had 1 sq mm of pituitary tissue in the plane of one section, and two patients had 2 sq mm in one section. All of the above patients were considered to have a functionally complete hypophysectomy. On the basis of previous experience we have estimated that a 10 per cent remnant of anterior pituitary tissue may be associated with entirely normal pituitary function.

We as well as others have observed that objective tumor regression may occur following incomplete pituitary ablation. Following pituitary stalk section, tumor regression has been observed in patients who were induced to lactate,[3] and in some such patients serum prolactin levels may actually be elevated.[19] In a recent report,[10] eight of nine patients who underwent transsphenoidal hypophysectomy were found to have normal serum prolactin levels postoperatively, and seven patients showed increases in serum prolactin following administration of TRH. Five patients with normal prolactin levels were observed to have objective tumor regression, and the authors felt that their observations raise serious doubts about the role of prolactin in inducing remissions. These incomplete hypophysectomies are not unlike the pituitary stalk sections in which the remissions are probably due to suppression of adrenal function. However, if some mammary cancers are dependent upon pituitary lactogenic hormones for growth, the potential benefit of complete hypophysectomy would presumably not be observed in patients with grossly incomplete hypophysectomy. It is our opinion that an incomplete hypophysectomy represents a technical failure and thus may not yield optimal therapeutic results.

Serum levels of estradiol, estrone, and estriol have been measured in patients who have undergone functionally complete hypophysectomies, and in all patients studied low levels of these hormones (5 to 40 pg per ml) have been detectable; they have also been detectable at similar levels after ovariectomy and adrenalectomy. Thus, surgical ablation of these endocrine glands fails to eliminate estrogens from the circulation.

Results of Hypophysectomy

Table 1 presents the results of hypophysectomy in the treatment of women with Stage IV breast cancer in two consecutive series of patients. In the first series of patients only five patients were surviving and three were still in remission at the time of evaluation; in the second series ten patients are still surviving and only two are in remission, so that the results are nearly complete. Objective remissions occurred in 42 per cent of patients in both series and the average duration of remissions was about 18 months. Survival time is significantly prolonged in patients who obtain remissions as compared with those who fail to benefit. However, survival time of both responders and failures is greater in the second series, which undoubtedly reflects the results of more effective chemotherapy.

These results are representative of what can be obtained in relatively unselected patients undergoing pituitary ablation. Hormone re-

Table 1. *Results of Hypophysectomy in the Treatment of Women with Stage IV Breast Cancer*

	FIRST SERIES[17] 89 PATIENTS	LATEST SERIES[2] 90 PATIENTS
Remissions (per cent)	42	42
Duration of remissions (months)	17+	18+
Survival (months)	26+	36+
No progression (per cent)	14	4
Duration of no progression (months)	4	15
Survival (months)	9	36
Failures (per cent)	44	54
Survival (months)	5	13

ceptors in the tumors were not available when these studies were carried out. When hypophysectomy is performed in patients with estrogen receptor positive tumors, the remission rate is 65 per cent, which is significantly higher than in unselected patients (see below).

Comparison of Hypophysectomy to Adrenalectomy

In the evaluation of our initial results with ovariectomy and adrenalectomy versus hypophysectomy, we felt that hypophysectomy was a more effective procedure, although the results were not unequivocal.[16] Other retrospective studies comparing these two procedures have shown little difference in the results.[4, 7] In the only prospective, randomized study comparing ovariectomy-adrenalectomy with hypophysectomy, Hayward et al.[5] reported a definite superiority of the results of hypophysectomy. These investigators found a significantly increased incidence of remissions, longer duration of the remissions, and longer survival for the responders with hypophysectomy. The results suggest that pituitary factors may play a role in maintaining the growth of some breast cancers.

Approaches to Medical Hypophysectomy

Antiprolactin and antiestrogen drugs have undergone clinical trials in an attempt to obtain antitumor effects comparable to those of endocrine ablative procedures. An ergot derivative, Lergotrile, effectively suppressed serum prolactin levels, but produced only minor antitumor effects in one-third of patients studied.[13] This drug does not affect the secretion of other pituitary hormones, and since human growth hormone is known to have lactogenic properties, it may be necessary to suppress both prolactin and growth hormone to obtain optimum antitumor effects.

Nonsteroidal antiestrogen drugs have also undergone clinical trials in the past several years and have been found to induce objective tumor regression in women with Stage IV breast cancer. Our re-

Table 2. *Results of Antiestrogens in the Treatment of Women with Stage IV Breast Cancer*

	PATIENTS		DURATION OF REMISSION (MONTHS)	NO. STILL IN REMISSION	SURVIVAL (MONTHS)	NO. STILL ALIVE
	No.	Per Cent				
A. 113 patients						
Remissions	56	50	15+	23	–	–
No progression	8	7	21+	2	–	–
Failures	49	43	–	–	–	–
B. First 39 patients						
Remissions	19	49	18+	3	29+	10
No progression	7	18	21+	2	28+	4
Failures	13	33	–	–	15+	1

sults (Table 2) with the antiestrogen drug, tamoxifen, are quite similar to those of surgical hypophysectomy in terms of incidence and duration of remissions.[8] Since this antiestrogen drug does not alter pituitary hormone secretion significantly, these results suggest that estrogens play the major role in maintaining the growth of hormone responsive breast cancer. The results also indicate that antiestrogens are the initial endocrine treatment of choice in women with Stage IV breast cancer.

We have also given antiestrogens to women who had previously obtained remissions from hypophysectomy and had relapses. Of 26 such patients antiestrogens induced objective tumor regression in six and arrest of disease in five with remissions averaging more than one year (Table 3). This represents additional palliation not possible by surgical ablation alone. In some of the patients who responded to antiestrogens after hypophysectomy, we retested pituitary function and found that prolactin and growth hormone were undetectable in the serum, although estrogens were detectable in low concentrations (see above). This suggests that estrogens can stimulate tumor growth in the absence of the pituitary gland perhaps by a direct action on the tumor.

Table 3. *Effects of Antiestrogens after Surgical Hypophysectomy*

	PATIENTS		DURATION OF REMISSION (MONTHS)	NO. STILL IN REMISSION
	No.	Per Cent		
Remission	6	23	15+	2
No progression	5	19	17	0
Failures	15	58	–	–

Table 4. *Results of Hypophysectomy after Antiestrogen Therapy*

	RESPONSE TO TAMOXIFEN (12 PATIENTS)	NO PROGRESSION ON TAMOXIFEN (3 PATIENTS)	FAILURE TO TAMOXIFEN (12 PATIENTS)
Remissions	6	0	2
Duration of remission (months)	11+	–	11
No. still in remission	3	0	0
No progression	2	0	0
Duration of remission (months)	9	–	–
Failures	4	3	10

Hypophysectomy after Antiestrogen Treatment

On the possibility that pituitary hormones may also play a role in stimulating the growth of some human breast cancers, we have performed hypophysectomy in 27 women who were initially treated with tamoxifen and either failed to respond or had a remission followed by relapse (Table 4).[8] Of 12 patients who intially responded to tamoxifen, six had objective remissions and two showed no progression following hypophysectomy. Of 12 patients who failed to benefit from antiestrogen, two obtained objective remissions after hypophysectomy. Of three patients who appeared to have an arrest of disease during tamoxifen therapy, all subsequently failed to benefit from hypophysectomy. These preliminary results suggest that pituitary hormones may also play a role in maintaining the growth of some human breast cancers.

Selection of Patients for Hypophysectomy

In our early studies of hypophysectomy, we observed that premenopausal women who obtained a remission from ovariectomy had a high incidence of response to subsequent hypophysectomy. This has continued to be our experience over the years, and about 90 per cent of women who initially responded to castration have subsequently obtained remissions from hypophysectomy, whereas only an occasional patient who failed to benefit from ovariectomy later resonded to hypophysectomy. Other clinical features were also shown to have predictive value, such as the age of the patient, the free interval between mastectomy and recurrence, and the response to additive hormone therapy; but this information was of little value in deciding on therapy for the individual patient, and hypophysectomy was undertaken with only a 40 per cent expectancy that it would be of value in the majority of patients.

Following the initial demonstration by Jensen et al.[6] that measurement of estrogen receptors in the primary or metastatic tumor tissue had predictive value for the response to adrenalectomy, we confirmed that these measurements were also useful in selecting patients for hy-

pophysectomy.[15] In the past few years we have used estrogen receptor measurements when available to select patients for hypophysectomy. In 34 patients with estrogen receptor positive tumors, 65 per cent had remissions, which was significantly higher than the response rate of 41 per cent in 147 patients without receptor measurements.[8] None of six patients with estrogen receptor negative tumors responded to hypophysectomy, although two of six patients with borderline receptor values obtained remissions from hypophysectomy. We feel that estrogen receptor measurements are useful in selecting patients for hypophysectomy.

We have also investigated the usefulness of measurements of progesterone receptors in the tumor tissues as a means of predicting the response to hypophysectomy.[9] If both estrogen and progesterone receptors are present in the tumor, there is a higher incidence of response to hypophysectomy (about 80 per cent); however, if estrogen receptors are positive and progesterone receptors are negative in the tumor, there is still an appreciable response rate to hypophysectomy (about 40 per cent). Thus, at present, progesterone receptor measurements are not of practical value in selecting patients for hypophysectomy.

We have recently reported that prolactin receptors are also detectable in about 50 per cent of human breast cancers.[14] There is no correlation between the presence of prolactin receptors and estrogen receptors, and they are present in both estrogen receptor positive and negative tumors. Preliminary clinical correlations suggest that prolactin receptor measurements will not improve the usefulness of estrogen receptor results in predicting the response to antiestrogen therapy. We are now investigating whether prolactin receptor measurements will be useful in predicting the response to hypophysectomy after antiestrogen treatment.

In view of the outstanding therapeutic results with the antiestrogen drug, tamoxifen, we are presently intially treating all patients with Stage IV breast cancer who are candidates for endocrine therapy with tamoxifen. Hypophysectomy is being performed in patients who have responded to antiestrogen followed by relapse where our preliminary experience suggests that about 50 per cent of the patients may obtain further benefit. We are continuing to explore the usefulness of hypophysectomy in patients who fail to benefit from antiestrogens, particularly if estrogen and/or prolactin receptors are present in the tumor tissue. It is hoped that prolactin receptor measurements in the tumor may prove to be useful in predicting the response to hypophysectomy, but this remains to be determined.

We no longer perform hypophysectomy in patients with advanced disease involving the liver, lungs, and central nervous system, and whose life expectancy appears to be a matter of a few weeks. Such patients are treated with a combination of antiestrogen and multiple cytotoxic chemotherapeutic agents as well as radiation therapy for lesions of the central nervous system. In those patients who respond favorably to such therapeutic maneuvers, hypophysectomy can be considered later as an additional therapuetic procedure if their general condition warrants.

At present, antiestrogens plus hypophysectomy appear to offer an optimal form of endocrine therapy for patients with Stage IV breast cancer. We are seeking an antigrowth hormone drug which, used in combination with antiestrogen and antiprolactin drugs, might yield a "medical hypophysectomy." Such a combination of antihormone therapy, if successful, would not only eliminate the need for endocrine ablative procedures, but would facilitate its use at earlier phases of the disease when the tumor burden is lower, which might result in longer periods of control of this systemic disease.

Summary

Transnasal, transsphenoidal microsurgical hypophysectomy is a useful therapeutic procedure for patients with Stage IV breast cancer which can be performed in selected patients with minimal morbidity and mortality. Functionally complete hypophysectomy can be accomplished with regularity, and anything less than this is considered to be a technical failure despite the fact that remissions may occur after incomplete hypophysectomy. In view of the recent outstanding results with antiestrogen therapy in patients with breast cancer, we recommend this as the initial treatment in those patients who are good candidates for endocrine therapy. Hypophysectomy has been shown to induce improvement after antiestrogen treatment, particularly in those patients who have had an initial response to antiestrogens as well as in a few patients who failed to benefit. Estrogen receptor measurements in the tumor tissue have been shown to be useful in selecting patients for hypophysectomy as well as for antiestrogen therapy. Prolactin receptors have been found in about 50 per cent of human breast cancers, and their potential usefulness in selecting patients for hypophysectomy is being explored. Hypophysectomy is a definitive therapeutic procedure that should not be used as a last resort in the terminally ill patient.

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Pregnancy and Breast Cancer

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The occurrence of malignant neoplasms of the breast during pregnancy and lactation presents therapeutic problems with which few surgeons have experience. Indeed, the incidence is so low that many surgeons may practice a lifetime and never face the problem. Few institutions have great experience in the management of the coexisting conditions.

A number of authors, however, have addressed themselves to the problem. It is not our intent based on five successful outcomes to do more than point out that therapy can be successful with conventional treatment. A complete summary of the literature is outside the scope of this presentation. Although many of the older articles documenting success and failures may be outmoded by newer diagnostic and therapeutic techniques, they serve to focus attention on the dilemma of the pregnant or lactating patient with breast cancer. Among the excellent articles often quoted in the literature, those by Diekamp and Donegan[9, 10] contain extensive bibliographic references that are sufficiently extensive to include all important and controversial points for even the most demanding clinician.

Although there is widespread disagreement, a recurrent theme in most articles is the concept that breast cancer is more virulent in its progression in young women. In fact, there is considerable evidence that breast cancer behaves similarly in the young and the aged patient.[8]

INCIDENCE

Over 90,000 new cases of breast cancer are discovered yearly in the United States. Although most patients with such cancers will have

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Supported in part by National Cancer Institute Contract NO1-CB-43990.

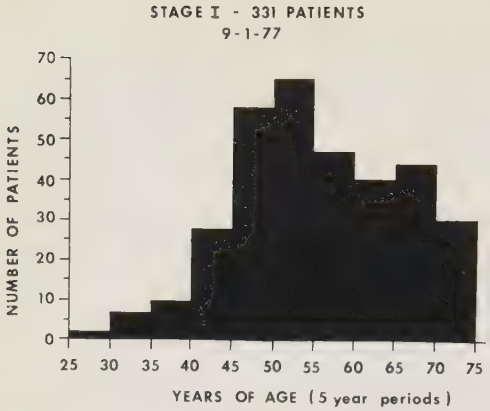

Figure 1. Age distribution of Stage I breast cancer in 331 patients is shown for 5 year periods from September 1, 1974 to September 1, 1977 in the Case Western Reserve University study.

presenting symptoms after their childbearing years are over, breast cancer will develop in a number of women immediately before, during, and after pregnancy.[4, 28] In 1956, White and White[41] reported the incidence of breast cancer among eight obstetric services. A total of 93 women among 300,860 pregnancies were diagnosed as having breast cancer, an incidence of 3 per 10,000 pregnancies. Of all breast cancers, 2.8 per cent are associated with pregnancy.[40]

In a prospective, randomized, clinical adjuvant trial of patients with breast cancer among 10 cooperating institutions, we have found that treated breast cancer patients younger than age 40 with both Stage I and Stages II and III (Figs. 1 and 2) represent 5.7 per cent and 12 per cent respectively of the 331, and 196 patients being followed during the first three years of the study. Figure 2 also depicts the tendency for the women younger than 40 to have more advanced disease ≥ four positive nodes). These data confirm findings of others that the

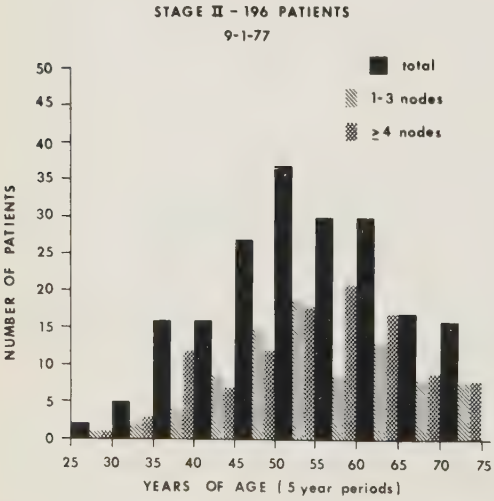

Figure 2. Age distribution of Stage II breast cancer in 196 patients from September 1, 1974 to September 1, 1977 in the Case Western Reserve University study is shown. Nodal involvement is shown for a 5 year period.

disease peaks at age 50, but continues at a relatively high level to age 75, the cut-off point for patients entering our adjuvant treatment protocol.

Cooper[6] reported on 7381 patients treated for breast cancer, of whom 593 (8 per cent) were younger than 40. Mueller[24] noted 49 patients with breast cancer younger than 30 (1.4 per cent) in his series of 3558 women. Wallgren,[38] reporting on cancer of the breast in women younger than 30 in Sweden from 1958 to 1968, found 75 patients less than 30 years of age with proven mammary cancer among 30,854 women with breast cancers (0.24 per cent). Peters[29] identified associated pregnancy in 3.8 per cent of 7136 breast cancer patients.

Lynch,[20] in his survey of the role of genetic factors, has pointed out a number of ethnic and possible associated endocrine relationships in breast cancer. The following five are emphasized:

First, cancer of the breast is six times more prevalent in North America and Europe than in Asia and Africa. Japanese women migrating to the United States have an increased rate of breast cancer compared with that of other native women who remain in Japan. In Hawaii the breast cancer in descendents of Chinese and Japanese women who have lived there for two to three generations is comparable to that of Caucasians in the same area and of the same age.

Second, a woman who becomes pregnant for the first time after age 30 is more likely to have undergone tumor induction prior to the pregnancy.

Third, lactation in native Japanese women has a protective effect, although other studies compared with controls show no apparent difference in risk.

Fourth, there is a reduced risk among women undergoing surgical menopause prior to age 40.

Last, an increased breast cancer risk appears to be associated with women who experience early menarche and in those who undergo a later natural menopause.

From these data, it can be seen that the disease is of a low order of incidence in pregnant young women, but for the 3 in 10,000 in whom the disease develops, certain therapeutic, moral, and social issues must be faced.

The important questions in regard to pregnant or lactating women with proven cancer of the breast are:

1. How should the pregnant women with breast cancer be treated?
2. Is waiting for the termination of pregnancy indicated or even desirable before mastectomy is performed?
3. Does accepted treatment by today's standards alter the life expectancy of the women?
4. If the woman is pregnant at the time of diagnosis or subsequent to mastectomy, is termination of pregnancy indicated?
5. Should the surgeon plan to castrate surgically the women with treated breast cancer for therapeutic reasons or primarily to prevent future pregnancies?

The prognosis for patients in whom breast cancer develops during pregnancy and lactation is generally poorer than that for other women.

Peters[30] has pointed out that timing of treatment in the pregnant patient is important. She noted that survival of patients treated for breast cancer in the early trimesters of pregnancy was higher than that of patients in whom treatment was not initiated until the latter half of the pregnancy, a point emphasized by others.

Peters and Meakin[30] observed that when primary breast cancer (Stages I to III) was treated during the first half of pregnancy, 13 of 27 (48 per cent) survived 5 years, whereas of those patients treated during the last half of pregnancy, only 3 of 22 (14 per cent) survived 5 years.

A number of both obvious and more obscure mechanisms must be considered in the poorer prognosis of breast cancer complicating pregnancy. For about a century it has been observed that pregnancy has an unfavorable effect on the survival of patients with breast cancer. Similar observations have been observed in animals with experimental mammary cancers.[10]

The occurrence of a number of related changes must be considered as part of the physiologic alterations of pregnancy. From the clinical standpoint, breast enlargement tends to shield breast masses from the examining fingers. The accompanying vascular and lymphatic changes often allow early growth and dissemination before the disease can be detected. As pointed out by Lacassange,[19] the endocrine changes stimulating mammary cancer in mice, and the beneficial effects of oophorectomy in many cases of disseminated disease have focused attention on endogenous hormones.[10] It has been well documented that striking rises in estrogen production occur during pregnancy, as manifested by increases in urinary excretion of estrone, estradiol, and estriol during this time.[10, 15, 29, 37]

Accompanying the increased production of estrogen is a two-to three-fold increase in corticosteroid levels. Particularly striking is the marked rise in plasma cortisol. Its possible effect on host resistance to a growing tumor through reduced cellular immunity, particularly of the circulating T lymphocytes, appears to be important.[37] The mechanism that permits fetal implantation apparently is related to an impairment of cellular immunity. This also seems to depress the host's resistance to malignant neoplasms and its containment of the latter by normal protective mechanisms. Increases in prolactin levels may play a role. McGuire[7] has demonstrated prolactin receptors in a mammary cancer which is deficient in estrogen receptor.

Jensen,[17] McGuire,[21, 22] and others[23, 27] have reported clinical correlations between estrogen receptor findings and the subsequent response to endocrine therapy of Stage IV mammary carcinoma. This breakthrough has allowed a more rational use of hormonal manipulation therapy, which includes antiestrogen drugs, oophorectomy, adrenalectomy, and hypophysectomy. In the previously mentioned clinical trials underway in Cleveland, estrogen receptor values have been determined in most of the breast cancers studied. The majority of the determinations have been made in a single laboratory (Dr. William McGuire, San Antonio, Texas), although a number have been analyzed in affiliated hospital laboratories. Figure 3 depicts estrogen receptor

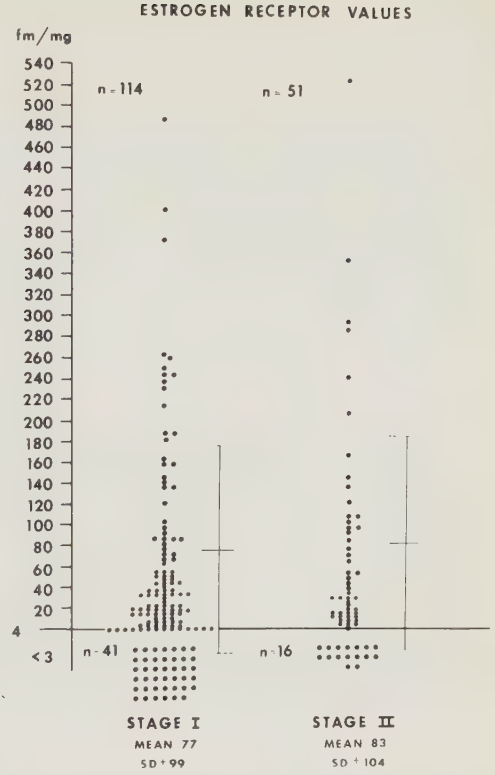

Figure 3. Estrogen receptor data are shown in femtomoles per mg of protein of breast cancer tissue for the first 155 Stage I and 67 Stage II patients in the Case Western Reserve University study. Values 4 and above are considered to be positive; values below 4 are considered to be negative.

values in femtomoles per mg of protein of breast cancer tissue in 115 Stage I patients with breast cancer, and in 51 Stage II patients early in our series with no apparent significant difference in more advanced disease with axillary node involvement. As our own study enlarged (Fig. 4), the trend appears to be the same, but with wider deviations. McGuire[18] has recently pointed out that estrogen receptor values may be of value in the prognosis of treatment failure in breast cancers, with greater recurrences in estrogen receptor negative tumors. Although endocrine and physiologic changes in pregnant and lactating women certainly are important risk factors in accelerated growth of

ESTROGEN RECEPTOR VALUES

	STAGE I	STAGE II
NUMBER OF PATIENTS	331	196
RANGE OF fm/mg protein	0 - 591.9	0 - 1512
MEAN	55.3	85.6
SD ±	± 87.7	± 166

Figure 4. Estrogen receptor data of 331 Stage I and 196 Stage II breast cancer patients from September 1, 1974 to September 1, 1977 in the Case Western Reserve University study, are depicted.

mammary cancers, it seems logical to look elsewhere to explain the poorer prognosis of such patients.

It appears that the prognosis of breast cancer is improved with earlier diagnosis and treatment, but it is also apparent that too often a significant delay occurs in diagnosis and treatment. Donegan[10] has compared the 5 year survival of operable pregnant or lactating patients from a variety of sources and periods. It is readily seen that the number of patients with axillary nodal involvement is still abysmally high, indicating advanced disease at the time of diagnosis, with subsequent low 5 year survival. Rissanen[32, 33] and Peters and Meakin,[30] however, have pointed out that early breast cancers were not appreciably less curable in pregnant patients when matched with those in women of comparable age. Unfortunately, the numbers are small in most series, but it is important to note that early diagnosis and treatment before axillary spread are potent factors in long-term survival.

The case histories of five patients treated at University Hospitals of Cleveland by one of us (F.M.B.) are presented to illustrate long-term survival following mastectomy associated with concurrent or subsequent pregnancies. Three patients were pregnant at the time of mastectomy. Two delivered normal infants and in one patient the pregnancy was terminated. One patient conceived and delivered a normal infant after mastectomy, after which she was sterilized. One patient, gravida III, para II, conceived 18 months following mastectomy, underwent therapeutic abortion and tubal ligation, and is now nearly 5 years postmastectomy without evidence of recurrent disease.

CASE REPORTS

Case 1

This patient presented at age 40 years with a one year history of a mass in the tail of Spence of the left breast. She underwent biopsy on 7-6-59 and pathologic tissue examination demonstrated a scirrhous carcinoma. Radical mastectomy was performed 7-10-59 and 30 nodes were negative. In 1961 at the age of 41 she became pregnant and spontaneously aborted. Four years later at the age of 45 (1965) she delivered a healthy female infant. Subsequently a right radical mastectomy was performed on 10-23-67 and 26 nodes were free of tumor. The patient was last seen in follow-up on 1-9-78. There was no evidence of recurrence.

Case 2

This 35 year old white female was four months pregnant when she presented with a one year history of an upper inner quadrant left breast lesion, which was 3 by 4 cm in size. Biopsy was performed on 8-20-62 and demonstrated infiltrating ductal carcinoma. Left radical mastectomy was performed and 3 of 23 nodes were positive. Termination of the pregnancy was recommended, and on 9-1-62 the patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Adjuvant radiation therapy was performed to the chest wall and axilla. One year later the patient developed symptoms of pericardial effusion and tamponade. She underwent pericardial biopsy and windowing on 10-28-63. No tumor was found in the pericardial fluid or the biopsy specimen. The effusion was therefore attributed to radiation percarditis. On 10-7-75 the

patient was last seen in follow-up and there was no evidence of recurrence at that time.

Case 3

This patient presented at 35 years of age with a five year history of "cystic mastitis" and a mass 1.5 cm in size above the nipple on the left breast. She underwent wide excisional biopsy on 10-19-67 and permanent sections demonstrated ductal carcinoma. She underwent left radical mastectomy on 10-20-67 and 29 nodes were negative. Her last normal menstrual period was 10-3-67 and it was not realized that she was pregnant at the time of the operation. Gestation was allowed to proceed to term and on 6-30-68 the patient delivered a healthy female infant. Right breast biopsy was performed on 11-28-69 for a mass 2 cm in size located in the upper outer quadrant, and pathology showed lobular cystic hyperplasia and mazoplasia. Last follow-up was 1-23-78 and there as no evidence of reccurrence.

Case 4

This patient was 35 years old when she presented on 1-7-69 with a three month history of dark brown discharge from the left nipple. Papanicolaou smear showed atypical cells. She had had three children previously and was six months pregnant at the time. No mass was palpable on examination. The patient underwent biopsy for presumed intraductal papilloma on 1-8-69 and permanent sections ultimately demonstrated noninfiltrating ductal carcinoma. Left modified radical mastectomy was performed on 1-10-69 and 25 nodes were negative. The primary lesion was noted to be in the upper outer quadrant and was 6 mm in diameter. The patient delivered a healthy female infant on 4-11-69 after induction of labor. An elective tubal ligation was performed at that time. She was last seen in follow-up on 1-4-78 and there was no evidence of recurrence.

Case 5

This 37 year old patient, gravida III, para II, was admitted to the hospital on 5-9-74 with a one and one-half week history of an asymptomatic mass 2 cm in diameter in the upper outer quadrant of the right breast. She had taken oral contraceptives for the six years prior to the admission and intermittently for six years prior to that. Biopsy was performed the next day and frozen section revealed carcinoma. A modified radical mastectomy was performed. Final pathologic diagnosis was infiltrating adenocarcinoma and 23 nodes were negative. The patient was advised not to become pregnant, but accidentally conceived, and on 12-5-75 underwent therpeutic abortion and laparoscopic tubal ligation. Gestation was judged to have progressed nine weeks at that time. She was last seen on 3-14-78 and there was no evidence of recurrent disease.

A number of authors have noted a better than average survival rate of breast cancer patients who later became pregnant. In Peters'[29] reported group of 129 patients in whom pregnancy occurred subsequent to mastectomy, 54 per cent survived 5 years even when pregnancies occurred within 6 months of mastectomy. The 5 year survival of 87 patients who became pregnant subsequent to mastectomy was compared with the 5 year survival of 1992 premenopausal women according to clinical staging. In Stages I, II, and III, there was an improved survival of the subsequently pregnant patients over those in the nonpregnant group. If one can accept that pregnancy following mastectomy has a favorable influence on breast cancer survival, and eliminate natural selection, it would seem feasible to allow more pregnancies to go to term when additional children are desired.

TERMINATION OF PREGNANCY

Our series is so small that we can make no decision on whether abortion should be carried out at the time the diagnosis of cancer is determined. Most authors agree that abortion has little value in terms of long-term survival. Haagensen[11, 12] concurs that with negative nodes the prognosis is favorable following mastectomy. He does indicate that with early pregnancy it would seem reasonable to abort as quickly as possible. White[40] and Randall[31] state that abortion does not benefit the subsequent course of breast cancer. In Randall's article it was emphasized by Schmitz that because the pregnancy should not affect the risk of surgery to the mother, immediate radical mastectomy should be performed. It also was emphasized that physicians should treat the cancer and ignore the pregnancy.

Most opinion based on rather scant data suggests that a decision to proceed to premature delivery by cesarean section or induced labor depends on the patient's wishes for a child and the imminence of term. It should be emphasized that there is no evidence that continued gestation represents a threat to the unborn child. Cancer cells that traverse the placenta and involve the fetus are practically unheard of.[35] Chemotherapy, however, is hazardous to fetal development and there is a strong risk of fetal anomalies with both antimetabolites and alkylating agents. Therefore, if mastectomy is done early in pregnancy and positive nodes necessitate adjuvant chemotherapy, the pregnancy should be terminated.

Cheek[5] reviewed the literature and pointed out that mammary cancer during pregnancy and lactation is often advanced when the primary diagnosis is made, and in up to 50 per cent of the patients it may have reached an inoperable stage at that point. Although he agreed that the question of abortion or termination of pregnancy remains unsettled, it should, when advisable, be carried out in the first trimester or the first half of the pregnancy. He emphasized that in those who underwent mastectomy and in whom positive nodes were found on pathologic examination, it would not be advisable to superimpose pregnancy.

All reviewers agree that delayed diagnosis on the part of physicians is a key factor in the poor survival rate following mastectomy. Therefore, an earlier diagnosis must be made, followed by prompt evaluation and surgery.

Most obstetricians who find breast masses in early pregnancy tend to regard them with only modest suspicion. Actually, they are right 9997 times out of 10,000. We believe, however, that any mass that appears during early or late pregnancy, and cannot be attributed to any other disease process, should be investigated. Whenever possible, consultation by a surgeon knowledgeable in breast disorders should be sought. If there is any question regarding the true nature of the mass, prompt diagnostic methods should be employed. Although mammography can be used with proper shielding of the fetus, the increased density of the gestational mammary tissue makes accurate diagnosis difficult. It would, therefore, seem logical to utilize needle aspiration and biopsy when localized lesions present as suitable targets. In more obscure lesions, surgical biopsy under

local anesthesia presents little risk to the mother or fetus and allows more suitable tissue for histologic examination. The latter method should be employed more often in doubtful lesions.

BREAST CANCER AND LACTATION

The development of breast cancer during lactation is less clear cut. Most series combine pregnancy and lactation data difficult to separate. It is generally agreed that in nonpregnant, nonlactating women, a 1 cm breast cancer (based on cell kinetic data of doubling times of 60 to 100 days) has been present for upwards of 2 to 3 years, and perhaps longer. The influence of the hormonal changes of pregnancy, however, may accelerate normal growth patterns. Therefore, the presence of any mass during pregnancy and lactation should arouse suspicion.[36] Surgical aspiration or excisional biopsy should be readily utilized to rule out carcinoma in the lactating patient.

Ing[16] studied breast feeding and its relationship, if any, to the development of a subsequent breast cancer. He conducted an interesting study involving the Chinese Tanka who live on the coastal waters and rivers of Southern China. The women breast feed only with the right breast, probably for convenience, because the opening of the clothing is on the right side. This study of the postmenopausal Tanka women who developed breast cancer indicated that the risk of cancer was significantly higher in the unsuckled breast, i.e., the left. From these findings, the author suggests that breast feeding may help to protect the suckled breast against cancer. He also compared the laterality of breast cancer in Chinese women in Hong Kong. In women who had breast fed unilaterally, he found an increased incidence of breast cancer in the unused breast, lending further credence to his study of the Tanka women. The relationship of this information on the development of cancer subsequent to lactation and breast feeding in women of the Western civilization is only speculative. By choice, many American women do not breast feed. Breast cancer can and does, however, occur in many multiparous women with strong histories of breast feeding.

PREGNANCIES SUBSEQUENT TO MASTECTOMY

There is rather clear-cut unanimity of opinion that the prognosis of young women undergoing mastectomy for cancer *with* involved axillary nodes is of such gravity that subsequent pregnancies are contraindicated. Early recurrence must be expected, although is not inevitable.

With negative nodes by pathologic examination, the prognosis for long-term survival is improved and subsequent pregnancies appear reasonable. Cooper and Butterfield[6] studied 7381 patients treated for breast cancer. Five hundred ninety-three patients were less than 40 years of age, and of these, 40 women became pregnant following mastectomy. Of these patients, 32 were treated more than 5 years prior to their study. Of 24

Stage I patients (negative nodes), 22 survived 5 years. Only two of eight patients with Stages II and III disease survived 5 years. Eleven patients had more than one pregnancy; of these, eight survived 5 years. This retrospective study was conducted with the use of two matched controls for each patient in the study group. Insofar as this study could be controlled, Cooper and Butterfield concluded that in patients with Stage I disease who have had mastectomies, there is no evidence to indicate an adverse effect of pregnancy on 5 year survival.

In 1937, Harrington[13] reported on 55 patients in whom pregnancy occurred subsequent to radical amputation of the breast. He also pointed out many long-term survivals without recurrences in this group, but on theoretical grounds tended to advise against further pregnancies after mastectomy.

White[39, 40] addressed himself to this problem and found among 25,159 breast cancer patients, 191 who conceived after mastectomy. He pointed out that the gross survival rate of patients in whom pregnancy followed mastectomy is comparable to those women who never became pregnant.

Similar data have been presented by Holleb and Farrow.[14] Austin[2] recommended a delay of at least 3 years after mastectomy before pregnancies, and then only for those patients with negative nodes. For patients with positive nodes at the time of mastectomy, he recommends a waiting period of 5 years, certainly not an unreasonable period. If there is no evidence of recurrence by then, clinical examination and roentgenographic evaluation with bone survey, bone scan, and mammography of the other breast would help to assess the curability of the previous mastectomy.

Rissanen,[32] in a reported series of 53 patients who became pregnant following mastectomy, found 41 patients (77.4 per cent) who survived 5 years; 28 were Stage I, 20 were Stage II, and 5 were Stage III. Most of his reported patients had undergone mastectomy followed by radiation therapy to node-bearing areas.

Applewhite et al.,[1] in his study of 655 patients of child-bearing age (45 years and under), also concluded that pregnancy following mastectomy for cancer of the breast did not substantially alter the survival rate of those patients.

PROPHYLACTIC CASTRATION

Although in the past prophylactic castration has been advocated to prevent future pregnancies in the younger patient with breast cancer, there is little evidence that such a therapeutic modality results in longer survival.

In theory, elimination of ovarian production of estrogen in the premenopausal woman might delay growth of disseminated cancer cells. In fact, the elimination of such a stimulus may allow most host defense mechanisms to contain growth or induce cytotoxic effects. Without question, therapeutic castration long has been observed to have such an effect on a significant number of patients with Stage IV disease.

Donegan,[10] however, has pointed out that several clinical trials in the United States have failed to justify the procedure.

The often quoted Nissen-Meyer[25] study of radiation castration, although apparently helpful to the postmenopausal group, was inconclusive in terms of survival in the premenopausal group.

In any event, prophylactic castration is unimpressive to date. It may have a place, however, in the patient with positive nodes and elevated estrogen receptor levels in the tumor.

Pearson[26] has advanced the possibility that antiestrogen drugs might also be effective in such cases. A clinical trial along these lines would seem justified.

In reviewing the data[3, 12] regarding subsequent pregnancies in breast cancer patients treated by mastectomy and showing no axillary spread, it would appear justifiable to allow selected women desiring further children the opportunity to conceive. It must be pointed out, however, that a successful pregnancy does not guarantee nonrecurrence of the cancer, and all factors must be weighed by both the husband and wife in their desire to have children. Few couples would welcome a child, only to have the mother die and deny the child maternal care.

Here a suitable delay of 2 to 3 years following mastectomy, along with vigorous diagnostic evaluation for recurrence, prior to the pregnancy would seem prudent.

SUMMARY

Breast cancer in association with pregnancy and lactation is rare, but presents a therapeutic problem of considerable magnitude. The outlook for such patients is less favorable than that of nonpregnant, nonlactating women, probably because the stage of the disease is more advanced when it is discovered. The most significant factor in the poorer prognosis is physician delay in diagnosis and therapy.

When mastectomy is carried out early in pregnancy, the operation can be as effective as in nonpregnant women of the same age groups. It is emphasized that when pregnancy and breast cancer are found concurrently, prompt therapy for the cancer should be undertaken.

Interruption of pregnancy in nondisseminated breast cancer is of little value. If pregnancy is near term when the diagnosis of disseminated breast cancer is made, the desire of the husband and wife for a child should be considered. A modest delay in therapy to allow for delivery probably has no deleterious effect.

Castration should be withheld and used only for the patient with metastatic disease. There may be a place for prophylactic castration in the treatment of disseminated disease, but its role is yet to be clearly defined.

Subsequent pregnancies in a patient with axillary spread at the time of mastectomy are contraindicated, because of the high rate of treatment failure and decreased rate of survival. In patients desiring future pregnancies following mastectomy, a period of observation of at least 2 years seems wise. At the end of that period, if clinical evaluation, laboratory

values, roentgenographic studies, and isotopic bone scanning are negative for disseminated disease, subsequent pregnancies seem safe.

Prompt evaluation of any breast mass found during pregnancy and lactation should be carried out by needle or operative biopsies under local anesthesia.

Although the prognosis of the pregnant or lactating woman with breast cancer is generally favorable, numerous long-term survivals are encountered in those women who undergo prompt mastectomy early in pregnancy.

The former pessimistic outlook for such patients seems unjustified. With modern methods of diagnosis and treatment, therapy can be effective and successful.

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Bilateral Breast Cancer

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The importance of the other breast when cancer is found in the first has been a subject of considerable controversy, especially as related to the following matters: the determination of whether a cancer in the other breast is metastatic or primary; the frequency of primary cancers in the second breast, whether simultaneous (synchronous) or subsequent (metachronous); the influence that a second primary cancer in the opposite breast makes on the survival of the patient; the psychologic and physical importance of the remaining breast to the patient after the first has been removed for cancer; and the way in which the other breast should be managed.[20-23, 25, 27, 32, 35, 38, 45, 48-50]

Primary or Metastatic Determination

A cancer of the breast can metastasize to the breast on the opposite side by permeation of lymphatics across the midline or by dissemination through the bloodstream. Since cross metastasis may be the first sign of systemic spread, it is of obvious importance to know if a cancer in the second breast is primary or malignant. However, despite the combined use of clinical and histologic evidence, in many cases the decision can be difficult.

Credit for establishing the first set of criteria for the recognition of multiple primary cancers is given to Billroth,[44] who in 1869 postulated that two or more coexistent neoplasms could be regarded as independent primaries only if: each has its own characteristic histologic appearance; the tumors are separate and located in different organs; and each produces its own separate metastasis. Neither these criteria nor the more liberal ones developed by Warren and Gates[55] in 1932 are fully applicable to the problem of bilateral breast cancer.

Cutler[6] has emphasized the fact that marked histologic differences are rare and that the diagnosis of an independent primary lesion in the other breast usually rests on histologic changes in the breast around the tumor and on clinical evidence. From the clinical standpoint, Haagensen[14] regards a contralateral carcinoma as a second primary if

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there is no clinical evidence of local spread across the midline or of distant metastasis and if the second breast lesion is solitary.

A carcinoma in the second breast should be considered as an independent primary if it is distinctly different in histologic type from the carcinoma of the opposite side or if it is shown histologically to be noninvasive while the contralateral lesion is invasive. Otherwise, the following criteria are utilized to determine whether a lesion in the other breast is primary or metastatic.

NUCLEAR DIFFERENTIATION. If the degree of nuclear differentiation of the lesion in the second breast is distinctly greater than that of the lesion in the first breast, then it is considered to be a primary.

ADJACENT TISSUE CHANGES. The lesion in the second breast is judged to be primary if foci consistent with site of origin of the cancer are different in the two lesions, or if one shows the presence of pronounced epithelial hyperplasia in the noncancerous duct system while the other does not.

CONTIGUOUS IN SITU CARCINOMAS. In primary tumors, contiguous in situ carcinomas is the rule, while this is not so in metastatic tumors. An exception to this is medullary carcinoma around which in situ changes are not expected.

LOCATION. Metastatic cancers most often appear in the fat that surrounds the breast nearest the midline or in the fatty tail. Second primary cancers, in contrast, occur in the breast parenchyma and are most often located in the upper outer quadrant but not in the fatty tail.

CLINICAL EVIDENCE. A cancer in the other breast is usually considered to be an independent lesion if there is no evidence of local or regional spread or of distant metastasis and if the cancer arises five or more years after the lesion in the first breast.

Incidence of Bilaterality

In 1945 Foote and Stewart[13] stated that "the most frequent antecedent of cancer of one breast is the history of having had a cancer in the opposite breast." While there is no question that the incidence of bilateral primary breast cancer is of significance, the reported incidence of both the simultaneous and subsequent types is of considerable variance.

Incidence of Simultaneous (Synchronous) Bilaterality

In the past the discovery of a simultaneous primary cancer in the other breast was based on the finding of a clinically palpable lesion in it. The incidence of clinically detectable simultaneous primary cancers in the other breast ranges from 0.2 to 2 per cent with an average of 0.5 per cent.[35]

These figures are considerably higher today based on the finding of occult, preclinical carcinomas, both noninvasive and invasive, by breast x-ray films, and by random biopsies of the other breast.

By preoperative mammography, Egan[34, 50, 57-59] found that 3 to 4 per cent of patients with a clinically detectable lesion on one side also had an occult carcinoma on the other.

Random biopsies of the other breast, as pioneered by Urban,[38, 50] have demonstrated a considerable number of preclinical cancers in it. In a series of 954 random biopsies of the other breast done on a consecutive series of 1204 patients undergoing mastectomy for a primary cancer in the first breast, Urban[38] found simultaneous cancers in 119 patients (12.5 per cent) and atypias in another 88 patients (9.2 per cent). Of the 119 carcinomas, 54 (46.2 per cent) were invasive and 64 (53.8 per cent) were noninvasive; 207 patients (22.4 per cent) had either atypia or cancer.

In a series by the author[32, 33, 38] of 321 random biopsies of the other breast done on a consecutive series of 500 patients with carcinoma in the first breast, 24 (7.5 per cent) occult, simultaneous, primary cancers and another 49 (15.3 per cent) atypias were found. Of the 24 carcinomas, 10 (41.7 per cent) were invasive and 14 (58.3 per cent) were noninvasive. Seventy-three of the 321 patients (22.7 per cent) had either atypia or cancer.

Others[12, 18, 46] using similar techniques had reported rates ranging from 4.5 to 7.3 per cent. McDivitt[41] pointed out that the difference in reported detection rates by empirical contralateral biopsy seemed to correlate with the size of the specimen removed, and, of course, with the diligence of the examining pathologist. Those with the greatest success obtain biopsies averaging a maximum of 4 to 5 cm in diameter, whereas those who do a token biopsy with little tissue have a low yield. The similarity in the combined percentages of atypia and cancer in the Urban and Leis series of 22.4 and 22.7 per cent respectively, and the differences in the percentage of carcinomas found in the two series of 4.5 and 7.5 per cent and in the percentage of atypias of 9.2 and 15.3 per cent, might rest in the pathologic interpretation between precancerous mastopathy and in situ carcinoma.

The use of these other modalities for detection beyond clinical examination would seem to indicate that the incidence of bilateral simultaneous primary breast cancer could be as high as 12 per cent. Of course, the question that is still unanswered is what percentage of the noninvasive cancers found, with these modalities, would go on to become invasive if they were left alone.

Incidence of Subsequent (Metachronous) Bilaterality

The reported incidence of a patient developing a subsequent primary cancer in the remaining breast after the first has been removed for cancer ranges from 1 to 14.3 per cent in various series,[7, 35, 45, 46] with an average of about 7 per cent. A number of factors are responsible for these striking differences:

LENGTH OF FOLLOW-UP. The incidence of cancer developing in the other breast increases at a rate of about 1 per cent per year of survival.[45] The longer the follow-up, the higher are the percentages of cancers developing in the second breast. Series with long-term follow-ups (20 plus years) will obviously have a higher incidence than those with short-term follow-ups, as shown in a recent review of 2734 patients enrolled in the National Surgical Adjuvant Breast Project,[17] and

followed from 1 to 67 months with a yield of only 52 cases (1.9 per cent).

CALCULATIONS OF PATIENT'S PROGNOSIS. The incidence of subsequent cancer developing in the remaining breast, in most reports, is based on the entire number of patients in the series. However, the absolute survival rate for all stages of breast cancer is only about 60 to 65 per cent for 5 years and 45 to 50 per cent for 10 years.[26, 29, 32, 33, 51-53] Many patients do not live long enough to have a great percentage of developing cancer in the other breast. If only patients with early cancer and good prognosis for long-term survival are considered, then the observed rate of bilaterality would be considerably higher.

BREAST YEARS VERSUS PATIENT YEARS. Patients followed with only one breast had only one half the risk of that for the general population for developing cancer in it; thus the risk would be doubled if breast years instead of patient years was used in recording bilaterality rates.[14] Robbins and Berg[45] estimated that the risk of a patient developing cancer in the remaining breast was about five times that for the general population.

VARIATION IN REPORTING STANDARDS AND PATHOLOGIC INTERPRETATION. Noninvasive cancers have a higher incidence of bilaterality than do invasive cancers,[2, 11, 16, 43, 50] and the most common of these, lobular carcinoma in situ, has a reported bilaterality as high as 30 to 40 per cent.[22, 23, 25, 49, 51] However, some centers[14] do not consider lobular carcinoma in situ to be a true cancer and call it lobular neoplasia. Elimination of these cases from a series would obviously result in a lower incidence of subsequent bilaterality.

Furthermore, a lesion considered to be a noninvasive carcinoma in one center may be regarded as a precancerous mastopathy in another, with a resulting difference in bilateral cancer rates. Finally, the difficulty in distinguishing between primary and metastatic cancer, and the possibility of a second breast lesion being considered metastatic without adequate investigation, could result in a difference in the reported incidence of subsequent reported primary cancers in the other breast.

ASSIDUITY OF FOLLOW-UP. Too often the follow-up of the other breast is not careful and the diagnosis of the cancer in it is not made early. It is conceivable that there could be an occult invasive carcinoma or a nondetected clinical one in the remaining breast that could by metastasizing be responsible for a patient's death but go unrecognized.

High-Risk Group

Every patient who has had a carcinoma in one breast has some increased risk for developing a subsequent primary carcinoma in the other. However, there is a subgroup of patients who have an especially high risk. This subgroup includes patients whose initial cancer in the first breast carried a good prognosis for extended survival, and whose age and constitutional status did not exclude at least a 20 year normal life expectancy. Thus patients under 50 years of age, in good health, with early cancers (Stage 0 and 1) that are noninvasive or with an

invasive type that is not prone to metastasize (adenoid cystic, tubular, colloid, medullary with lymphoid infiltrate, papillary, and comedo with minimal stromal invasion) are at high risk for developing a subsequent primary cancer in the second breast.

Also in the subgroup are patients who have special features that indicate an increased risk of bilaterality. This includes patients with a close family history of breast cancer, especially if bilateral and premenopausal,[1, 31, 36] those whose cancers in the first breast were multicentric throughout the breast, and those who had evidence of precancerous mastopathy[24, 37] found on biopsy of the remaining breast.

Finally, those patients with a P2 or DY parenchymal type of pattern on radiographs of the remaining breast as described by Wolfe[56] in which diagnosis is very difficult owing to the dense parenchyma,[10] and those with an abnormal thermogram[4] will have to be included in the high-risk group. In the author's series[38] of 101 patients without adverse findings on clinical mammogram or thermogram of the remaining breast, who had that breast removed by simple mastectomy because they were in the high risk group for developing cancer, 17 unsuspected cancers (16.8 per cent) were found, of which 5 (29.5 per cent) were infiltrating and 12 (70.5 per cent) were noninfiltrating. Another 18 patients (17.8 per cent) had atypical changes consistent with precancerous mastopathy.

Depending on how these variable factors are used in determining the percentage of subsequent primary cancers in the other breast, the figure could be quite low or as high as 30 per cent. It is obvious that the total incidence of bilateral breast cancer is far higher than older statistics indicated and that it can be expected to increase as more efficient methods of detection and treatment become commonplace.

Influence on Survival of a Second Primary Cancer

Despite supposedly careful follow-up, the diagnosis of cancer in the remaining breast is often not made at an early stage.[35, 45] The statement that has been repeatedly made and recently reemphasized,[17] that the survival rate after a second primary cancer in the remaining breast is as good as the survival rate after the cancer in the first breast, has little meaning. The absolute survival rate for combined Stages I and II breast cancers is about 70 per cent for 5 years and 55 per cent for 10 years. Even if the cancer is Stage I, about 15 per cent of patients will not survive 5 years and 30 per cent will not survive 10 years.[22, 26, 29, 32, 33] There can be no question that the development of a primary cancer in the remaining breast deleteriously influences the survival of the patient. Robbins and Berg[45] noted that a second breast cancer acting in conjunction with the first cancer almost halved the expected survival of the patient after the time of its appearance.

Psychologic and Physical Importance of the Other Breast

Much has been made of the psychologic and physical importance of the other breast. Some authorities including Haagensen,[14] Herrmann,[15] Lewison,[39] and Lewison and Neto[40] believe that it has a strong

psychological support for many women who cherish it as a badge of motherhood, as a sign of femininity, and as an important psychosexual symbol. It is true that some women seem to cherish it, but generally it remains as a useless and largely nonfunctioning organ. Few women are willing to show it as a badge of sexual enhancement alongside their opposite mastectomy scar, and equally few women allow it to be used during the act of love making. If the woman should become pregnant and if she were allowed to deliver, it would be rare that the patient would allow or the doctor condone its use for nursing.

There is no question that some women are adamantly opposed to losing their other breast. In some there is a strong psychological attachment to the remaining breast, which also offers the patient a definite physical support, especially if breast reconstruction has been done on the mastectomy side. Many women, however, about three to six months after surgery for cancer in one breast begin to express a deep concern about their other breast. They complain of feeling a lack of symmetry, of feeling unbalanced, and of experiencing difficulty in getting a satisfactory external prosthesis, especially if the remaining breast is large and causes difficulty in dressing, bathing, and other movements. They are worried about pain, nodularities, and irregularities in the remaining breast, and express a marked anxiety about the chance of developing cancer in it and the influence that such a cancer would make on their survival.

Management of the Other Breast

There seems to be increasing agreement among many authorities that by removing one breast for cancer, one certainly does not remove the carcinogenic factors that caused it from exerting their same influence on the other breast, that the incidence of cancer in the second breast is significantly high, that there is a group of patients who have an increased risk of developing cancer in it, that it remains as a useless and largely nonfunctioning organ serving at best as a questionable psychosexual symbol, and that development of cancer in it would exert a deleterious influence on the survival of the patient.

The question that is still unanswered is what to do about it. We advise an approach combining several modalities.[38] A random biopsy is done on the opposite breast on all patients undergoing primary therapy for potentially curable cancer in the first breast, except in elderly patients or those with severe constitutional diseases. If a cancer is found appropriate therapy is instituted. If no cancer is found then the patient is followed very carefully by monthly self-examination of the breast, by physical examinations of the breast by her physician at least every six months, and by yearly x-rays of the breast, and if possible, by thermographic and ultrasonic examination. Only if the patient is in the high-risk group for developing cancer in the other breast is prophylactic removal by simple mastectomy advised.

Technique of Contralateral Biopsy of the Breast

If the other breast is without adverse findings clinically or on

mammogram, biopsy is done in the mirror image site of the lesion in the first breast; if this is not in the upper outer quadrant, then this area is also sampled, whenever possible, through a single incision, but if not through two separate incisions. If there are suggestive physical or mammogram findings in the other breast, then this determines the site of biopsy.

The incision, when possible, should be made along the natural dynamic wrinkle lines of Kraissl,[5, 19] which are concentric circles radiating out from the nipple and the areola, in order to get the best possible cosmetic results. The incision transverses but preserves the underlying skin, subcutaneous tissue, and fat down to the breast parenchyma. A fusiform piece of mammary parenchyma averaging a maximum of 4 to 5 cm in diameter is removed. The walls and margins of the biopsy cavity are carefully palpated for suspicious nodularities or thickening, and if any are found they are also excised. After careful hemostasis the wound is closed in layers without drainage. Preservation of the fat and its separate meticulous approximation prevents dimpling and deformity of the overlying skin and results in a satisfactory cosmetic appearance.

Prophylactic Contralateral Mastectomy

Routine prophylactic contralateral mastectomy has been occasionally advocated,[3, 43] but it is obvious that the adoption of such a policy would result in many unnecessary operations and have little influence on survival. We believe that the procedure should be reserved for women with a high risk for developing cancer in the remaining breast and it should not be done simultaneously; rather should be delayed for three to six months after the initial mastectomy to reduce emotional reaction and operative morbidity and to allow adequate time for evaluation of risk factors. Furthermore, it is about this time when many patients express a spontaneous concern about their second breast, thus providing an opportunity for an indepth discussion of the need for and advisability of its prophylactic removal.

Total mastectomy through a transverse incision is preferable to subcutaneous mastectomy in which all the breast tissue cannot be removed. If appropriate biopsies of the subareolar area are negative, then the areola skin and nipple base cut as a split-thickness graft can be banked in the inguinal area or some other convenient location for use in subsequent breast reconstruction. Since our patients undergoing prophylactic contralateral mastectomies were in the high-risk group for developing a subsequent primary cancer in the remaining breast, with early good prognostic cancers in the first breast, mastectomies on the original breast were done with lesser procedures than the standard radical mastectomy with preservation of at least the pectoralis major muscle. Because of this, we have been able to do bilateral breast reconstructions with satisfactory cosmetic results.

Summary

The true incidence of bilateral breast cancer, both simultaneous

and subsequent, is higher than older statistics indicate, and the frequency can be expected to increase as more efficient methods of detection and treatment become commonplace.

Furthermore, there is a subgroup of patients who have an especially high risk for having a second primary cancer in the other breast; if such a cancer develops it deleteriously influences the survival of the patient.

A rational approach to the management of the other breast is presented using contralateral biopsy as an added modality for detection and reserving prophylactic mastectomy of the other breast for those patients who are at high risk for developing cancer in it.

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Chemotherapy of Recurrent Breast Cancer

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Approximately half of the 91,000 new cases of breast cancer estimated to occur in the United States this year will eventually recur.[8] The median survival after this first recurrence is only seven months.[16] Even among patients with "local" recurrences, over 90 per cent will have simultaneous distant metastases.[6, 16]

Although patients with estrogen receptor positive tumors may benefit from hormonal manipulation, nearly one-half of breast cancer metastases lack this hormone receptor.[21] For these women and those who do not respond to endocrine therapy, cytotoxic chemotherapy can improve the quality[27] and duration[9] of survival.

This report reviews the status of chemotherapy in the treatment of recurrent breast cancer with emphasis on single drugs, combination agent regimens, and combined modality approaches.

SINGLE DRUG CHEMOTHERAPY

The development of effective drug combinations in Hodgkin's disease and acute lymphocytic leukemia depended upon recognition of the clinical activity and toxicity of several single agents. In breast cancer several drugs qualify as "building blocks" in the construction of active combination chemotherapy regimens and combined modality approaches (Table 1).

Alkylating agents exert their cytotoxic action by the formation of covalent bonds between adjacent nucleophilic groups of DNA. These bonds result in cross-linking and abnormal base pairing.[12] Among the alkylating drugs, cyclophosphamide is the most widely studied in recurrent breast cancer. It has been used orally and parenterally in a variety of dosage schedules with objective responses in 34 per cent of treated patients.[11] In addition to the myelosuppression and nausea and

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Table 1. *Single Agent Chemotherapy in Recurrent Breast Cancer**

	DRUG	RESPONSE (PER CENT)
Alkylating agents	Cyclophosphamide	34
	Nitrogen mustard	35
	Phenylalanine mustard	22
	Chlorambucil	20
	Thio-Tepa	30
Antimetabolites	Methotrexate	36
	5-Fluorouracil	26
	6-Mercaptopurine	14
Vinca alkaloids	Vincristine	21
	Vinblastine	20
Antibiotics	Adriamycin	35
	Mitomycin C	38
Miscellaneous	Hexamethylmelamine	28
	Dibromodulcitol	27
	Nitrosureas	15

*After Carter, S. K.: Chemotherapy of breast cancer. Treatment Reviews, 3:150, 1976. Copyright by Academic Press Inc., Ltd. (London).

vomiting seen with most drugs of this class, cyclophosphamide can cause hemorrhagic cystitis, particularly in underhydrated patients.

Phenylalanine mustard (L-Pam, Alkeran, Mephalan) produces responses in 22 per cent of patients with recurrent breast cancer.[11] The intermittent oral schedule of this drug has made it an attractive adjuvant to mastectomy,[17] but it probably is less effective in recurrent breast cancer than cyclophosphamide.

Antimetabolites act by inhibiting a metabolic process crucial to DNA synthesis. Methotrexate inhibits dihydrofolate reductase inhibitor resulting in a deficiency of folinic acid. It has been used in breast cancer with a variety of parenteral and oral dose schedules with an overall response rate of 36 per cent.[11] The major dose-limiting toxicities are mucositis and myelosuppression.

5-Fluorouracil inhibits thymidylate synthetase and produces tumor response in about one-fourth of breast cancer patients. A study comparing four different dose schedules did not demonstrate superiority of the traditional five-day loading schedule over weekly administration.[2]

Vincristine and vinblastine are derivatives of the periwinkle plant that act by inhibition of the mitotic spindle[12] and have response rates of about 20 per cent.[11] Vincristine is more widely used in the United States, possibly due to its minimal bone marrow toxicity. Neurotoxicity, however, may limit its chronic administration.

Of the antitumor antibiotics, doxorubicin hydrochloride (Adriamycin) is the most widely used. Its mechanism of action is thought to be

intercalation between DNA base pairs. It must be given intravenously, as skin sloughing may occur after extravasation.[28] A variety of dosage schedules have been used, but most oncologists favor a single dose of 50 to 70 mg per m^2 every three weeks. A Southwest Oncology Group Study demonstrated responses in 55 per cent of previously untreated patients.[19] Vomiting, alopecia, and reversible bone marrow suppression are common side effects. In addition, fatal cardiac toxicity may occur if the cumulative dose exceeds 550 mg per m^2. This severe cardiomyopathy may occur at lower doses in patients receiving mediastinal radiation therapy or cyclophosphamide. Recently, Myers et al. at the National Cancer Institute avoided this complication in mice by the simultaneous administration of an electron scavenger.[24] Whether such therapy in humans will prevent cardiomyopathy without compromising tumor response remains to be established.

Other antitumor antibiotics are not widely used in breast cancer. Although mitomycin-C may produce responses in one-third of patients, unpredictable bone marrow suppression limits its widespread use.[11]

The nitrosureas (BCNU, CCNU) are minimally active in recurrent breast cancer with an overall response rate of 15 per cent.[11] However, those drugs have generally been used in patients refractory to more traditional chemotherapy.

Two synthetic agents of some interest are hexamethylmelamine and dibromodulcitol. Both have response rates of about 30 per cent.[3, 10] Hexamethylmelamine is given orally and has only mild myelotoxicity. Neurotoxicity may be avoided by the simultaneous administration of pyridoxine. Dibromodulcitol is also given orally. Although it may act as an alkylating agent, cross resistance with cyclophosphamide is apparently not complete.[29]

COMBINATION CHEMOTHERAPY

The era of combination chemotherapy for recurrent breast cancer dates to 1963 when Greenspan reported responses in 60 per cent of women treated with methotrexate and thiotepa.[18] Six years later Cooper reported a 90 per cent response rate in 60 patients treated with a combination of five drugs (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisone) referred to as CMFVP (Table 2).[13] Several subsequent modifications of this regimen have been reviewed in detail by Carter.[11] In brief, the conclusions from these studies are as follows:

Table 2. *Combination Chemotherapy: The "Cooper Regimen"*

Cyclophosphamide	2.5 mg per kg per day orally
Methotrexate	25 to 50 mg per week intravenously
5-Fluorouracil	12 mg per kg per day intravenously × 4, then 500 mg per week intravenously
Vincristine	0.035 mg per kg per week intravenously
Prednisone	0.75 mg per kg per day orally

1. The combination of CMFVP results in higher response rates and longer survival than the sequential use of each of the five drugs as single agents.
2. No single variant of CMFVP is clearly superior. Two studies have suggested that continuous therapy may be better than intermittent therapy, but the differences are not statistically significant.[5]
3. No subsequent study has achieved the 90 per cent response rate noted by Cooper. Although differences in patient selection (e.g., disease-free interval and dominant side of involvement) and response criteria may explain some of these differences, most series report a response rate closer to 60 per cent.

The responsiveness of recurrent breast cancer to single agent Adriamycin chemotherapy prompted the development of several combinations containing this drug (Table 3). A comparison of Adriamycin and vincristine with CMF demonstrated response rates of about 50 per cent with both combinations.[15] The Adriamycin-vincristine group, however, had a long duration of response. Furthermore, these two regimens lacked cross-resistance, as about 25 per cent of patients failing one treatment responded to the other.

Combinations of cyclophosphamide, Adriamycin, and 5-fluorouracil have been tested by several groups including M.D. Anderson Hospital,[4] Memorial Sloan-Kettering Cancer Center,[14] and the National Cancer Institute.[7] These combinations have resulted in response rates of 61 to 82 per cent. The cumulative dose-limiting cardiomyopathy associated with Adriamycin, however, generally limits the duration of therapy with these combinations to 8 to 12 months.

In addition to variations of CMFVP and the above mentioned Adriamycin-containing regimens, other combinations are being evaluated. A Swedish study utilizing high dose methotrexate with citrovorum rescue, vincristine, Adriamycin, and cyclophosphamide reported 30 per cent complete remissions and 78 per cent complete and partial remissions.[20] The nitrosurea CCNU in combination with Adriamycin produced objective responses in 9 of 31 (29 per cent) patients failing CMFVP.[23] Two studies using another nitrosurea, BCNU, with Adriamycin and cyclophosphamide have demonstrated response rates of 44 and 50 per cent.[25, 26] Tormey et al. noted responses in 46 per cent of patients receiving dibromodulcitol and Adriamycin.[29]

In summary, although no single chemotherapy regimen can currently be considered optimal, many combinations have demonstrated significant tumor responses and improvements in patient survival. The future of chemotherapy in recurrent breast cancer will include further testing of combinations of existing drugs, search for new drugs, and integration of chemotherapy with immunotherapy and hormonal therapy (see below).

COMBINED HORMONAL-CHEMOTHERAPY

In 1966 Greenspan reported responses in 81 per cent of patients receiving a combined hormonal-chemotherapy regimen consisting of methotrexate, Thio-Tepa, testosterone, and prednisone.[19] Since hormones and cytotoxic drugs appear to have different mechanisms of ac-

Table 3. *Combination Chemotherapy in Breast Cancer: Some Regimens Containing Adriamycin*

INSTITUTION	ADRIAMYCIN	VINCRISTINE	CYCLOPHOSPHAMIDE	5-FLUOROURACIL	RESPONSE (PER CENT)
NCI, Milan[15]	75 mg/m² IV every 21 days	1.4 mg/m² IV on days 1 and 8	–	–	52
M. D. Anderson[4]	50 mg/m² IV every 21 days	–	500 mg/m² IV every 21 days	500 mg/m² IV on days 1 and 8	72
Sloan-Kettering[14]	30 mg/m² IV on days 1 and 8, every 28 days	–	60 mg/m²/day orally for 14 days	400 mg/m² IV on days 1 and 8	61
NCI[7]	30 mg/m² IV on days 1 and 8, every 28 days	–	100 mg/m²/day orally for 14 days	500 mg/m² IV on days 1 and 8	82

tion and toxicities, it is surprising that more combined modality trials did not develop until recently.

The Mayo Clinic reported a randomized study in 1977 comparing combination chemotherapy with cyclophosphamide, 5-fluorouracil, and prednisone given either with oophorectomy or as delayed treatment when progressive metastatic disease appeared after oophorectomy.[1] The group receiving combined hormonal-chemotherapy had a higher response rate and a longer duration of remission and survival than the group receiving sequential therapy.

A study at Emory University compared sequential versus concurrent therapy with diethylstilbesterol (DES) and combination chemotherapy (cyclophosphamide, Adriamycin, and 5-fluorouracil).[22] As in the Mayo Clinic study, patients receiving concurrent hormonal chemotherapy were more likely to respond to treatment for a longer period of time than patients randomized to sequential therapy.

Both the Mayo Clinic and the Emory University studies, however, did not utilize estrogen receptor status in patient selection. This critical variable will be analyzed in several ongoing combined modality studies. Acute Leukemia Group B is comparing oophorectomy versus oophorectomy plus cyclophosphamide versus oophorectomy plus CMFVP. A similar comparison of oophorectomy with or without CMF is under study at the National Cancer Institute. The Southwest Oncology Group is evaluating CMF with or without the antiestrogen tamoxifen in recurrent breast cancer.

An additional area of research lies in the addition of immunotherapy to combination chemotherapy and/or hormonal therapy. Several such studies are in progress, but to date the analysis of their results is incomplete. A detailed discussion of immunotherapy in breast cancer is contained elsewhere in this volume.

SUMMARY

Several chemotherapeutic agents given singly or in combination are capable of producing significant tumor regression in recurrent breast cancer. Such remissions improve both the quality and duration of life. To date, the most active combinations have been variations of Cooper's CMFVP therapy or regimens containing Adriamycin. Further improvements in survival may be realized from the addition of hormonal and/or immune therapy to these active combinations as well as from the development of new drugs.

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Breast Reconstruction Following Mastectomy

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With the public increasingly aware of the possibility of reconstructive surgery following mastectomy, the demands for such surgery increase. Patients' wishes aside, the first priority in malignant disease of the breast is to perform an adequate and, if possible, curative resection. Thereafter, one may consider reconstruction of the breast, hoping to achieve as near a normal cosmetic result as possible.

Most patients who are subjected to mastectomy will suffer an alteration in body image. Certainly concern for the loss of the breast should be less than concern with the loss of life, but mastectomy may adversely affect the psyche to varying degrees. This reaction varies from patient to patient according to age, social status, and social and economic background. As women become involved in the decisions about the surgical treatment of breast cancer, they too have more knowledge of the availability of reconstructive procedures, making it necessary for the general and reconstructive surgeon to maintain a close liaison and similar policies.

Before considering breast reconstruction, a number of questions must be answered. The first is whether any women should have reconstruction. There has been no evidence that a breast reconstruction lessens the prognosis or alters the natural course of breast cancer. Enough questions have been raised elsewhere in this symposium about the curability of these tumors. Ideally we try to reserve these procedures for patients with Stage I lesions — those women without detectable systemic metastases. These women are thus evaluated by scans of liver and bone, and by physical examination. Though occasional exceptions are made, women with metastatic disease are not often offered reconstructive surgery.

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"When in the selected case, should reconstruction be performed?" Arguments for and against immediate and delayed reconstruction exist. There are several problems with immediate reconstruction. There is a greater chance of hematoma, seroma, skin necrosis, infection, and loss of the prosthesis. While these are uncommon (less than 3 per cent), in perhaps 10 per cent the prosthesis will extrude through the skin after necrosis of skin flaps.[6] A second reason is that a woman who has lived with the results of mastectomy will be happier with less than perfect results of the reconstruction compared with the shapeless anterior chest wall that she lived with following her initial operation. For this reason, we encourage a delay in reconstruction for as long as possible. A further benefit for this delay is a more mature scar and more supple, pliable skin which will accept a larger prosthesis. Reconstruction is delayed for at least six months following mastectomy.

Having decided that reconstruction is indicated and then having waited the appropriate length of time, the next question is, "What procedure should be performed?" The answer to this is determined by the nature of the initial operation and the wishes of the patient and opinion of the plastic surgeon and general surgeon. The type of ablative operation that the patient has undergone influences significantly the reconstructive procedure. Simple or modified radical mastectomy requires a less extensive procedure than radical mastectomy for reconstruction. With the tendency to less radical operations, the task of the reconstructive surgeon has been considerably simplified. When simple and modified radical mastectomy has been performed, varying amounts of skin and underlying pectoralis major muscle remain. In this group, a one-stage procedure, namely, one-stage restoration of contour with reconstruction of nipple and areola, is frequently performed. Simultaneous contralateral breast reduction or correction of ptosis is done to maintain symmetry, but this is dependent on the patient's age and wishes.

GROUP A: SIMPLE AND MODIFIED MASTECTOMY

The one-stage operative reconstructive procedure is subdivided into four major steps: formation of contour, reconstruction of areola, reconstruction of nipple, and correction of contralateral asymmetry.

Formation of Contour

During the period of delay from mastectomy, the scar will have matured considerably, and a supple mobile anterior chest wall with the palpable underlying pectoralis major muscle should be present. The extent of laxity is assessed and similarly the contralateral breast is measured for the degree of hypertrophy and ptosis.

With the patient upright, the suprasternal notch, the midclavicular point, and the future submammary fold are identified and marked with methylene blue (Fig. 1). Thereafter, with the patient in the supine semirecumbent position, the submammary incision as previously

Figure 1. Preoperative markings.

demarcated is made extending deep to the pectoralis major muscle. A pocket is dissected by a combination of blunt and sharp dissection deep to the pectoralis major muscle, freeing the entire space deep to the pectoralis major muscle.[4] Tension will be experienced either in a transverse or vertical band, depending on the direction of the previous incision. This is the factor that limits the distention of the skin of the anterior chest wall. An inflatable prosthesis is inserted into the pocket deep to the pectoralis major muscle (Fig. 2). The size of the prosthesis

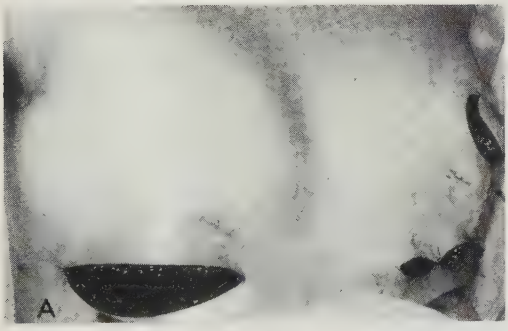


Figure 2. *A*, Subpectoral implantations. *B*, Implant in situ.

is determined by the size of the pocket. This is inflated within the limits of safety (as determined by the elasticity of the overlying tissue and scar). The wound is closed in layers, with suction drainage to the pocket.

Reconstruction of the Areola

Having restored the contour by subpectoral augmentation, if reconstruction of the areola is desired, the site of the nipple and areolar complex is determined by measurement from the suprasternal notch and by comparison to the normal side. The site is demarcated on the skin overlying the augmented breast. Areolar reconstruction may be provided by one of several techniques. The choice of technique will be determined by individual color requirements. Examination of the contralateral nipple-areolar complex will reveal a variance in color from pale pink to bright red to light brown to dark black, according to the pigmentation of the patient.

Circumstances are ideal if during the mastectomy the nipple-areolar complex had been banked on the anterior abdominal wall (Fig. 3).[11] In this situation, simple relocation by free grafting of the complex to the anterior chest wall provides excellent results. Smith, Payne, and Carney studied the incidence of nipple involvement in breast cancer and found an incidence of 12.2 per cent.[12] Involvement is more likely with: a primary tumor below the nipple, a multicentric tumor, a primary tumor greater than 4 cm, and involvement of four or more axillary nodes. To save the nipple areolar complex at the time of the initial ablative procedure, certain criteria must be fulfilled.

First, the lesion must be deep and distant from the nipple and areolar complex with no attachment to this structure.

Second, the nipple must be grossly free of disease and biopsies of nipple areola must be negative. The nipple-areolar complex will then be banked on the lower anterior abdominal wall for 6 to 18 months, awaiting retransplantation to the augmented reconstructed breast. During this period, the patient is observed to exclude the presence of local, regional, or distant recurrent disease.

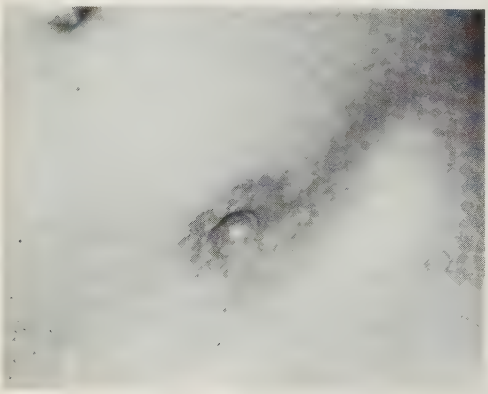


Figure 3. Banked nipple-areolar complex.

Although no case reports of transplanted breast cancer in a banked nipple have been documented, the number of procedures done are few and follow-up is limited. The area measured on the mound of the new breast is demarcated with methylene blue and the diameter for the aerola will vary from 35 to 42 mm, depending upon the size of the breast and the patient. This area is then de-epithelialized and prepared as the recipient area for the free grafting of the nipple-areolar complex from the lower anterior abdominal wall (Fig. 4). The nipple-areolar complex is harvested from the anterior abdominal wall (Fig. 5), completely defatted as a full thickness skin graft without any underlying subcutaneous tissue, and sutured into position to the recipient

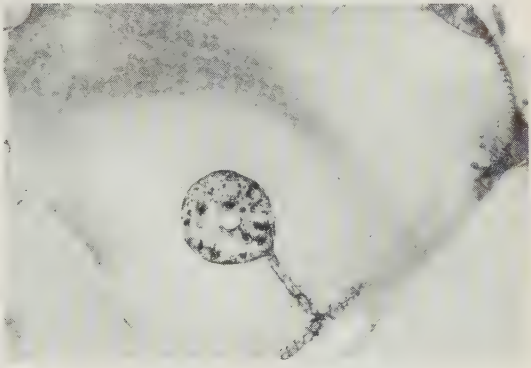
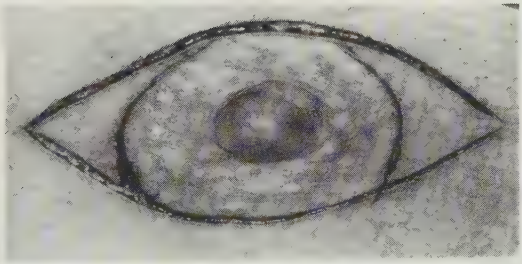


Figure 4. Deepithelialized recipient bed for nipple-areola graft.



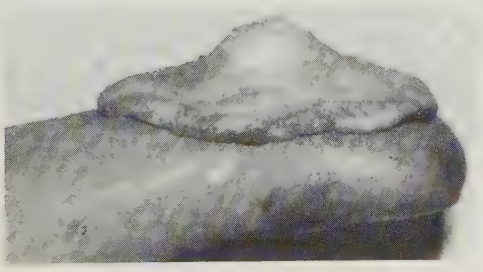


Figure 5. The nipple-areolar complex is harvested from the anterior abdominal wall.

de-epithelialized zone on the new breast (Fig. 6). A simple tie-over pressure dressing is applied. The take is excellent.

When no nipple-areolar complex is banked, several satisfactory alternate methods are available for reconstruction. The methods are:

AREOLAR SHARING TECHNIQUE FROM THE CONTRALATERAL BREAST. Areolar sharing will provide excellent color match for the neo-areolar complex. This may be performed as a split thickness skin graft procedure. The method initially described by Millard[10] was to harvest a split thickness skin graft from the areolar complex of the normal breast by use of a dermatome. The donor areola will spontaneously re-epithelialize within a period of 10 to 12 days and the split thickness skin graft provides excellent color match for the neo-areola. A similar procedure of areolar sharing may be provided from the contralateral normal areola where the diameter of the areola measures greater than 55 mm in diameter (Fig. 7).[13] In such cases of hyper-

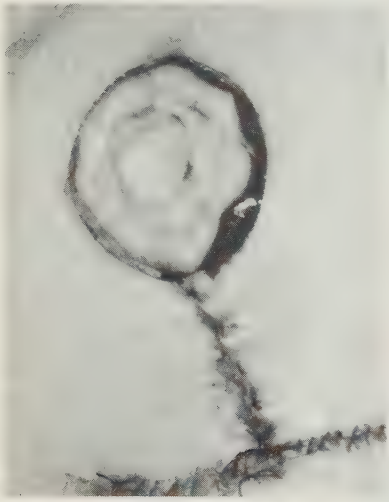


Figure 6. The nipple complex is transposed to the breast.

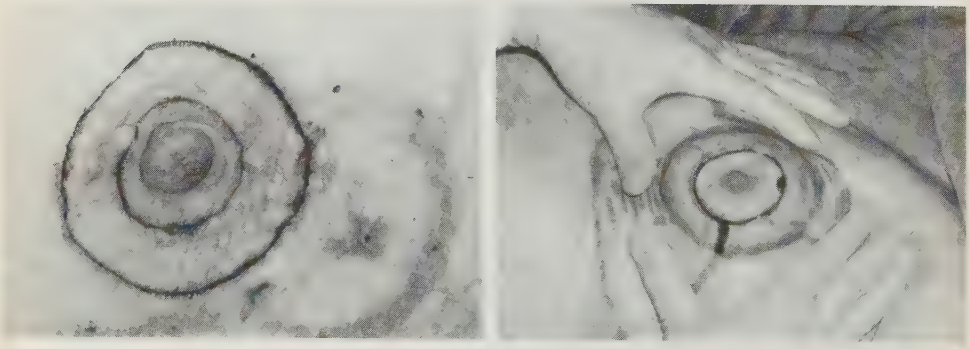


Figure 7. Areola sharing procedure by full thickness graft.

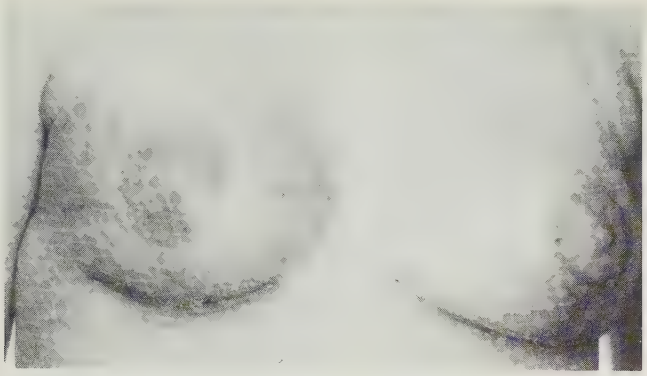


Figure 8. Result of areolar sharing.

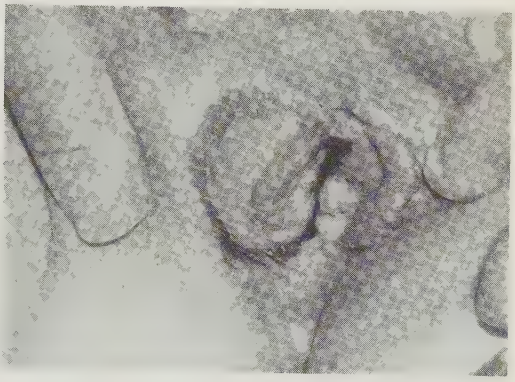


Figure 9. Site of vulval free graft for areola reconstruction.

trophy of the normal breast and marked distention of the areola, much of the areola can be harvested as a full thickness graft during the reduction procedure of the normal breast. The full thickness areolar skin harvested from the distended areola provides an ideal color match for neo-areolar reconstruction (Fig. 8). This full thickness skin graft is tailored into the de-epithelialized zone on the reconstructed breast and the take is excellent.

Vulval Graft. When there is insufficient skin on the areola for areolar sharing and the patient refuses violation of the existing normal areola, free vulval skin grafting or skin from the medial thigh provides excellent color match for the darker-skinned individuals (Fig. 9).[5] When the existing normal areolar complex is darkly pigmented, sufficient skin can be harvested from the labia minora, or a split thickness skin graft taken from the medial thigh can provide good color match for areolar reconstruction. It has been suggested that exposure of the skin graft from the medial thigh to ultraviolet light following the healing will provide deepening of pigmentation and allow for a closer color match with the normal side.

Close examination of the normal areola on the contralateral breast will reveal a varying number of Montgomery's tubercles. To simulate these tubercles, fragments are punched out on the cartilage of the ear and placed beneath the areolar graft. Two and 3 mm biopsy punches are used. An incision is made in the postauricular fold, the perichondrium is dissected, and the conchal cartilage of the ear is exposed. A disposable skin biopsy punch measuring 2 to 3 mm in diameter is drilled into the conchal cartilage and 8 to 10 cartilaginous punch specimens are harvested. These are dispersed at random deep to the areolar skin graft and provide an excellent simulation of the Montgomery's tubercles that exist on the normal areola (Fig. 10).

Reconstruction of the Nipple

In the case of a banked nipple-areolar complex, the protrusion of the nipple persists following relocation of the complex. However, when the nipple has not been banked, adequate protrusion of the nipple can be provided by a number of techniques:

1. The nipple sharing procedure is used when the contralateral nipple is hypertrophied and enlarged and it makes a very satisfactory composite nipple graft. A transverse resection of the distal nipple complex is made or a lateral wedge is excised and the donor nipple closed by direct approximation (Fig. 11). The composite graft is sutured into the central de-epithelialized zone of the areolar reconstruction and undergoes discoloration and revascularization is neovascularization be-

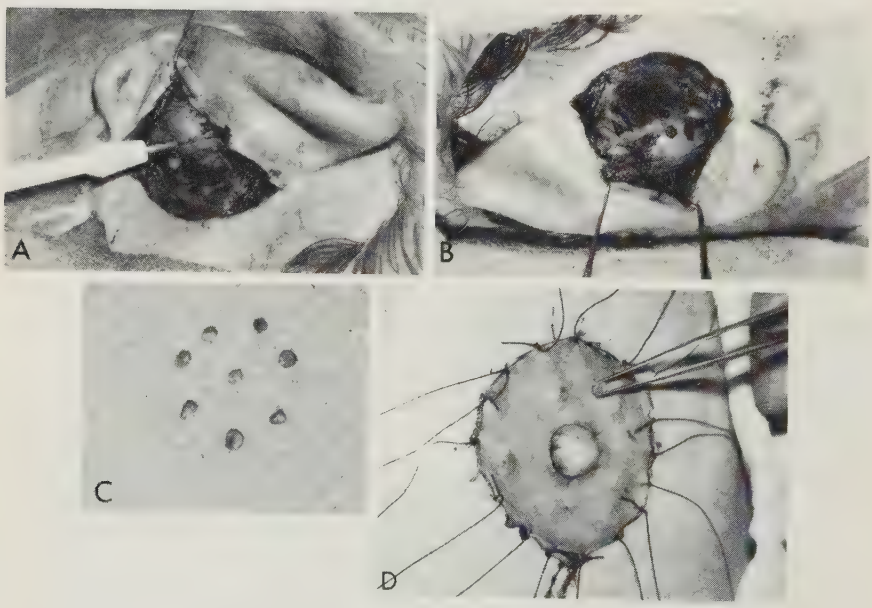


Figure 10. *A*, Conchal cartilage "punch" specimens for Montgomery's tubercles. *B*, Source of conchal cartilage grafts. *C*, Conchal cartilage grafts. *D*, Subareola insertion of conchal cartilage grafts.

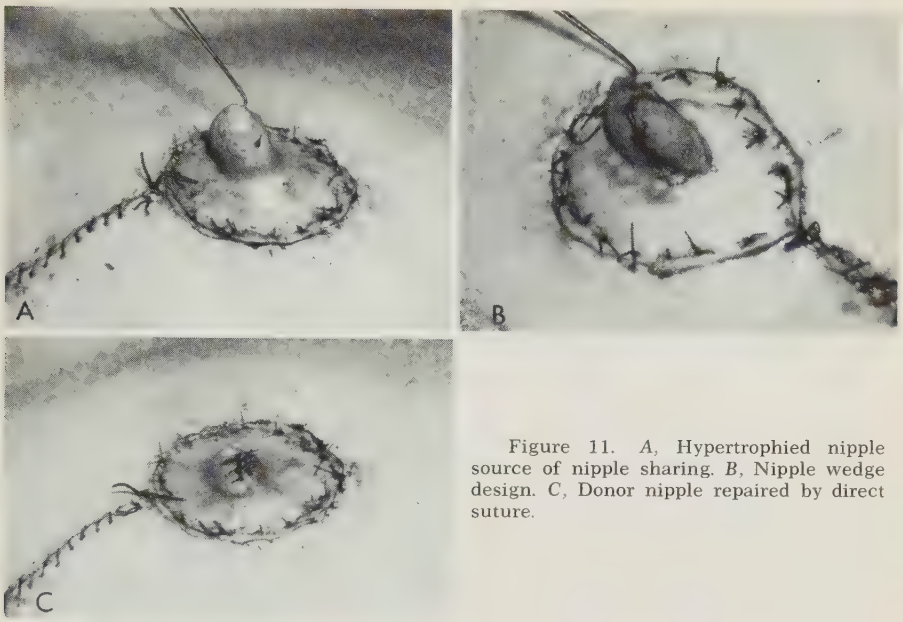


Figure 11. *A*, Hypertrophied nipple source of nipple sharing. *B*, Nipple wedge design. *C*, Donor nipple repaired by direct suture.

fore established in the composite graft. The results are generally excellent with permanent satisfactory protrusion of the nipple graft (Fig. 12).

2. When a nipple is not hypertrophied or when the patient does not wish a nipple sharing procedure, an excellent alternative is the use of the ear lobule composite graft. A segment of ear lobule provides a composite graft that closely similates a nipple protrusion, and the donor site heals with minimal inconspicuous scarring and no disfigurement.[1] A full thickness graft is harvested with a No. 11 BP blade from the lobule of the ear, measuring 5 to 10 mm at its greatest width. The lobule is unfolded, trimmed to the required shape and size, and sutured into position in the central de-epithelialized zone of the areola. Take is excellent and the protrusion is permanent.

3. Advancement techniques (V Y advancement and the Maltese cross) may be used to produce a satisfactory nipple-like protrusion (Fig. 13);[12] however, the long-term results have been disappointing with progressive retraction and flattening of the surgically created protrusion.

Correction of the Contralateral Asymmetry

Having restored contour by subpectoral implantation and having provided maximum augmentation, contralateral symmetry may be provided by reducing the size of the breast or by correcting its ptosis as the situation warrants. This will provide a better symmetry between the normal breast and the reconstructed side. Enough controversy persists among general surgeons regarding immediate biopsy and subse-

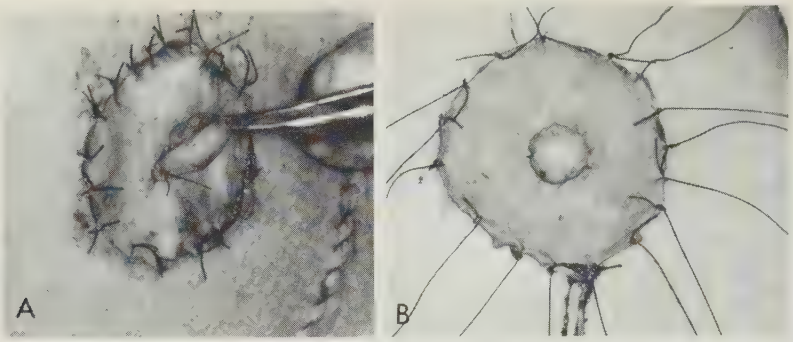


Figure 12. *A*, Composite nipple graft. *B*, Neo-nipple areola complex.

quent cancer of the contralateral breast without plastic surgeons becoming involved. Prior to any mammoplasty, a thorough examination of this breast by the general surgeon is mandatory, including xeromammography to exclude occult lesions. Opinions vary about how the second breast should be treated, and include simple mastectomy, subcutaneous mastectomy, reconstruction, and no treatment at all. These opinions are many but the data on which these are based are less. These controversies are discussed elsewhere in this symposium.

Except when the remaining breast is very small, augmentation of the reconstructed breast will not match the remaining normal breast. To obtain cosmetic symmetry requires some degree of reduction or cor-

Figure 13. Maltese cross of skin for 4 V-Y advancements.

rection of the ptosis. We employ the reduction mammoplasty technique described by McKissock (Fig. 14).[8] The extent of the correction or reduction mammoplasty is determined by comparing it to the augmented side, with the understanding that the augmented side can be increased in size by further inflating the prosthesis after three to six months once the skin of the anterior chest wall has stretched.

GROUP B: PATIENTS PREVIOUSLY SUBMITTED TO RADICAL MASTECTOMY

Radical mastectomy by definition usually removes more skin than simple or modified radical mastectomy as well as the pectoralis major and pectoralis minor muscles. Many patients who have had this procedure require a more complex reconstructive operation.

The cosmetic and functional deficits are greater and the infraclavicular depression resulting from ablation of the pectoralis major muscle are difficult to reconstruct. The long-term cosmetic results fall short of those in the previous group. Nevertheless, the principles of reconstruction are identical. Patients are encouraged to delay reconstruction for as long as possible. Thereafter, additional difficulties are presented to

Figure 14. *A*, Reduction mammoplasty technique described by McKissock. *B*, Transposition of the nipple on the superior and inferior pedicle. *C*, Right breast-nipple-areola reconstruction. Left breast reduction for symmetry.

the patient and her reconstructive surgeon. The major difficulty is to provide sufficient full thickness skin and subcutaneous tissue to the anterior chest wall, to allow for augmentation. Once this prerequisite has been fulfilled, the principles of reconstruction are as described above.

LAYING THE FOUNDATIONS FOR CONTOUR FORMATION

To provide full thickness skin and subcutaneous tissue after radical mastectomy, distant vascularized skin and subcutaneous must be "imported." The choice of reconstructive techniques again is predetermined by the nature of the radical mastectomy. We have identified three distinct groups of mastectomized patients: Group 1, radical mastectomy with vertical incision; Group 2, radical mastectomy with oblique incision; and Group 3, radical mastectomy with transverse incision.

Groups 1 and 2 may be dealt with by similar reconstructive techniques. The recent addition of the myocutaneous flaps to the reconstructive armamentarium[7] has allowed for one-stage transposition of full thickness skin and subcutaneous tissue to such patients.

Groups 1 and 2: Oblique and Vertical Scars (Fig. 15)

When oblique and vertical scars remain after radical mastectomy, a long thoracoepigastric myocutaneous flap will provide excellent and abundant soft tissue, for future restoration of contour.[2, 3] The flap is based medially on the rectus abdominus muscle, with the perforators from the superior epigastric artery providing "axial pattern" type vascular distribution to the thoracoepigastric flap. The flap is outlined along the submammary fold from the lateral edge of rectus abdominis to the anterior axillary fold and may measure 23 cm in length by 10 to 12 cm in breadth (Fig. 16). The flap is raised and dissected deep to deep fascia and is extended to the lateral border of the rectus abdominis muscle. The muscle may be transected inferiorly to make it easier to rotate the flap into the anterior chest wall. The scar from the previous ablation is excised, the defect recreated, and the flap transposed into position. The donor site of the thoracoepigastric flap may be suitably closed by direct approximation of the superior and inferior margins of the defect. This flap provides excellent, well vascularized soft tissue and skin cover. It is allowed to mature for three to six months. After this, the reconstructive technique may be similar to that outlined above to restore contour and create nipple and areola with correction of contralateral symmetry.

Group 3: Mastectomized Patients with a Transverse Scar (Fig. 17)

Patients previously subjected to radical mastectomy through a transverse incision requiring full thickness skin and subcutaneous tissues prior to augmentation may undergo reconstruction in a one-stage procedure by the latissimus dorsi myocutaneous flap.[3, 7]

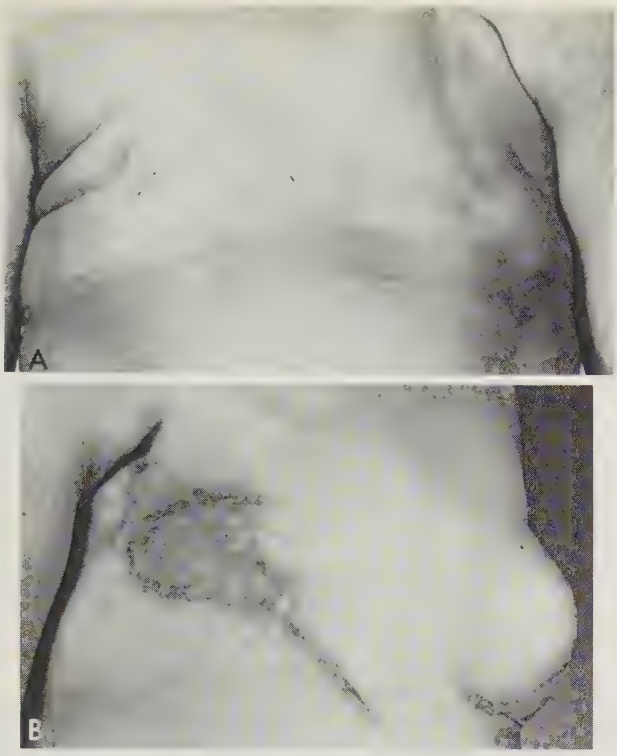


Figure 15. *A*, Vertical scars in a bilateral mastectomy. *B*, Oblique scar and graft after mastectomy.

The latissimus dorsi myocutaneous flap outlined on the lateral chest wall may measure 22 by 13 cm and is based superiorly on the underlying latissimus dorsi muscle with the axial vascular distribution of the thoracodorsal artery and vein (Fig. 18). The flap is raised, dissected, and transposed on its arteriovenous pedicle, to the axilla (Figs. 19 and 20). Prior to dissection of the latissimus dorsi flap, the axilla should be explored to document the presence of a patent thoracodorsal artery, for if the patient had previously been submitted to an axillary node dissection, this dominant pedicle may have been transected.

Having raised and dissected the flap on its axial pattern, the scar of the transverse incision on the anterior chest wall is excised and the flap is transposed. The donor area on the lateral chest wall may be closed by direct approximation. A similar period is allowed to elapse before the second stage.

CONCLUSION

The aim of breast reconstruction is to restore body image by providing symmetry and by simulating contour on the ablated side, a

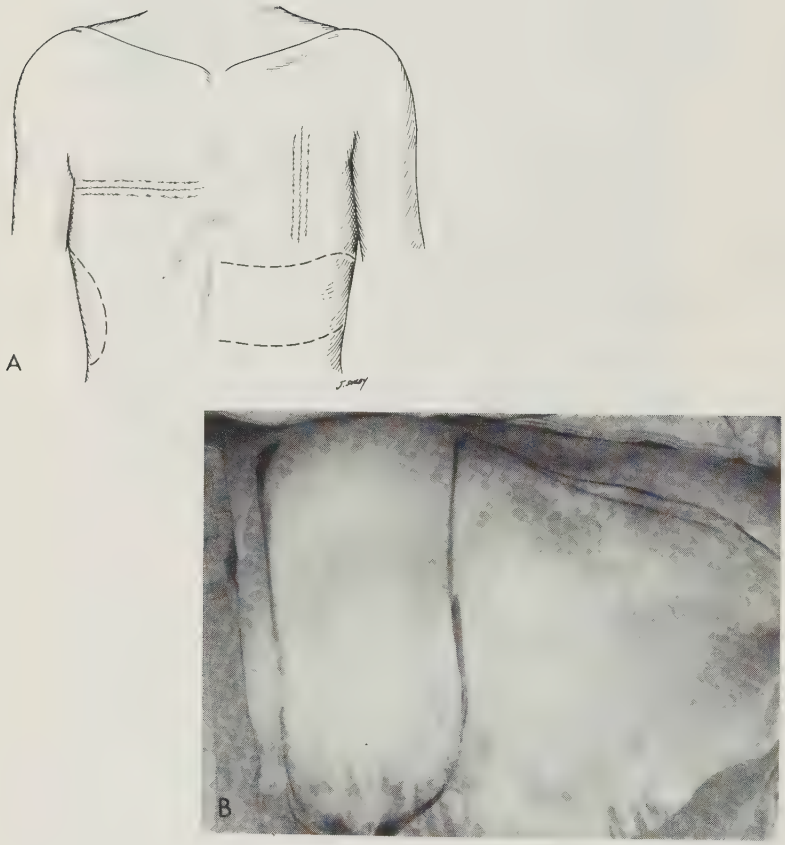


Figure 16. *A*, Design of myocutaneous flaps for provision of vascularized skin and subcutaneous tissue. *B*, Design of a thoracoepigastric flap.

Figure 16 *Continued.* *C*, Thoracoepigastric flap. *D*, Primary closure of the donor area of the transposed thoracoepigastric flap.

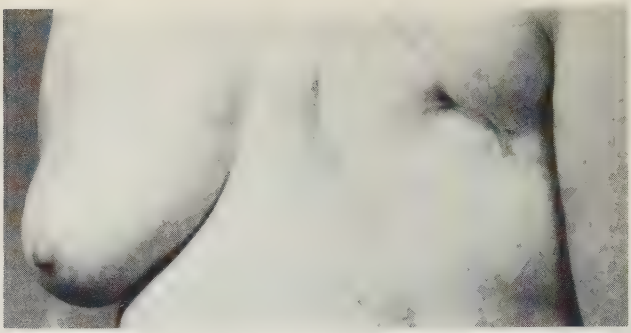


Figure 17. Transverse scar after radical mastectomy.

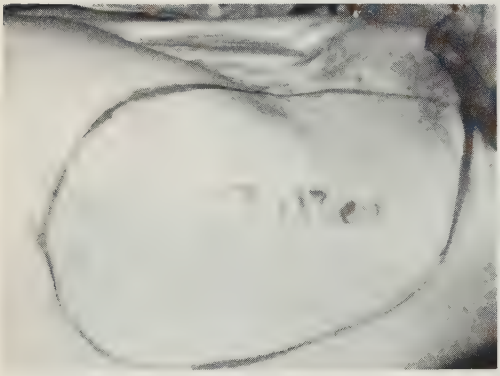


Figure 18. Design of a left latissimus dorsi myocutaneous flap.

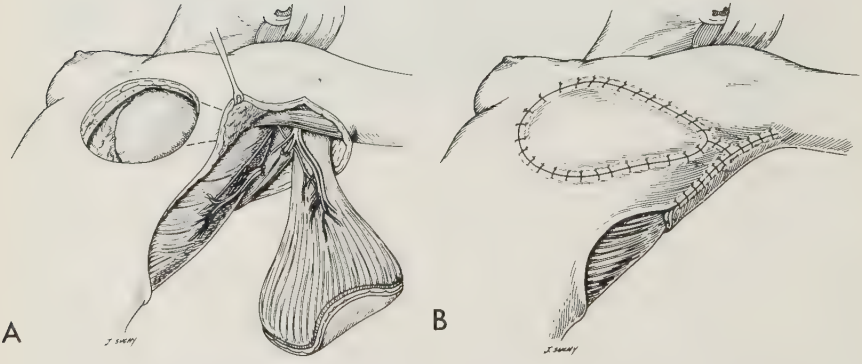


Figure 19. *A*, Latissimus dorsi myocutaneous flap showing arteriovenous pedicle. *B*, The flap is transposed into the chest wall defect.

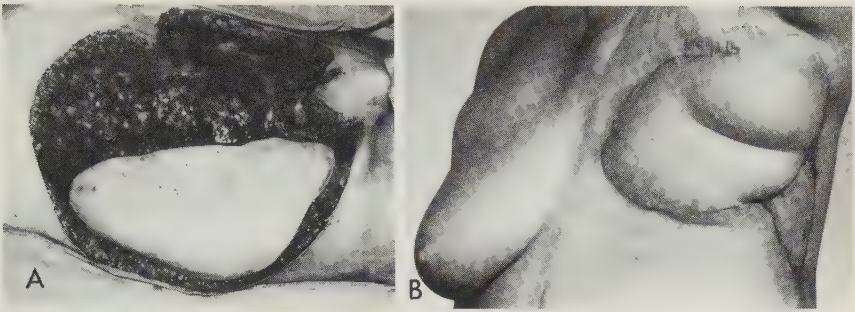


Figure 20. *A*, The latissimus dorsi myocutaneous flap is dissected. *B*, The flap is transposed to the anterior chest wall.

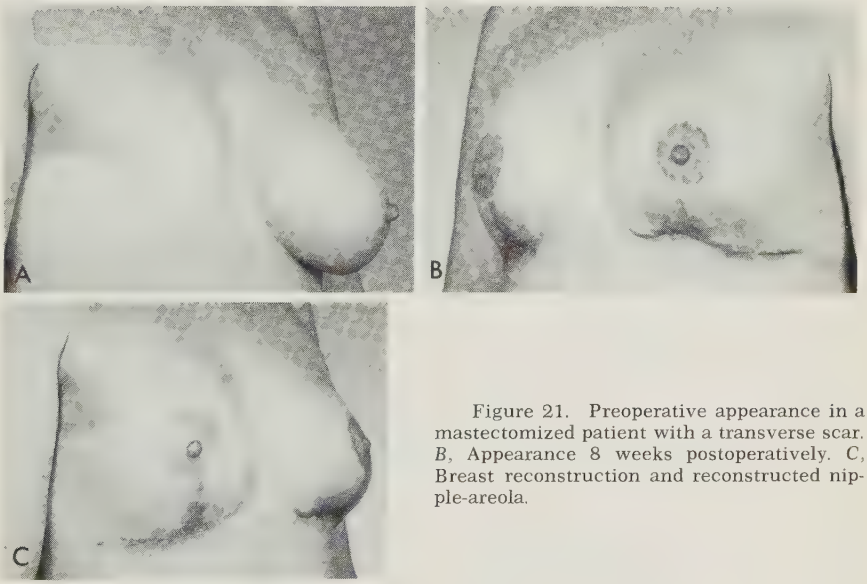


Figure 21. Preoperative appearance in a mastectomized patient with a transverse scar. *B*, Appearance 8 weeks postoperatively. *C*, Breast reconstruction and reconstructed nipple-areola.

nipple-areolar complex (Fig. 21). If patients wish to be restored, in most cases it is feasible. The procedure is delayed for as long as possible and thereafter a one-stage procedure is performed or, in the case of patients who have had radical mastectomies, a two-stage procedure is used after provision of a satisfactory foundation by the importation of vascularized skin and subcutaneous tissue by local myocutaneous flaps.

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The Rhomboid Flap and Partial Mastectomy

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Partial mastectomy with or without axillary dissection may be used as a primary treatment for breast cancer.[1] The operation has been praised and criticized and its results and indications are summarized elsewhere in this symposium.

A frequent shortcoming of partial mastectony is cosmetic deformity of the remaining breast either because of malposition of the nipple and areola or because of excision of large amounts of breast tissue. This deformity not only detracts from the esthetic result but may be one factor that limits application of partial mastectomy. To correct this shortcoming we have utilized the Limberg rhomboid flap in 15 patients. This report will decribe the technique and illustrate the results.

TECHNIQUE

The margins of excision are determined and these margins are then incorporated in a 60 degree rhomboid design with 60 degree angles. The design of the Limberg flap[2, 3] for partial mastectomy is created according to the classic description. The short axis of the defect (Fig. 1) is extended into the axilla to allow for exposure and dissection of axillary contents. The flap is then raised with full thickness skin and subcutaneous tissue and transposed into the defect, allowing the side (D-E) to be closed directly to (A-B).

The subcutaneous and subcuticular layers are approximated and suction drains are left in the axilla 24 to 48 hours. Patients are dismissed 48 to 72 hours postoperatively.

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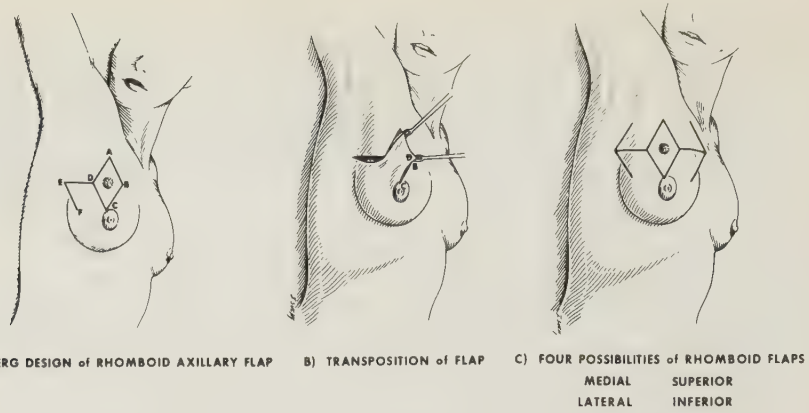

Figure 1. *A*, Design of the rhomboid flap. *B*, Its transposition into the defect created by excision of the rhomboid defect. *C*, Possible applications and extensions.

Four potential flaps may be created. The natural selection for upper quadrant breast lesions is to place the flap in the axilla to allow access for axillary dissection and to hide the scar. Figure 2, *A* to *E* illustrates the operative technique.

DISCUSSION

The technique of partial mastectomy usually involves a 4 cm skin ellipse around the tumor and excision of 5 cm of breast tissue around the primary tumor including pectoralis fascia. For lesions near the nipple or when excision of the breast and subcutaneous tissue leaves significant cosmetic deformity, the rhomboid flap may correct the deformity without changing the position of the areola and nipple. The technique is applicable for upper and lower, and outer quadrant lesions. This approach allows for in continuity axillary dissection. The cosmetic result three months postoperatively is shown in Figure 3. The lesion excised was above and lateral to the nipple. Earlier postoperative results are shown in Figures 4 and 5.

SUMMARY

The use of a rhomboid flap in segmented breast resection is described. This reconstructive technique allows large areas of the breast to be resected with minimal deformity and nipple-areola displacement.

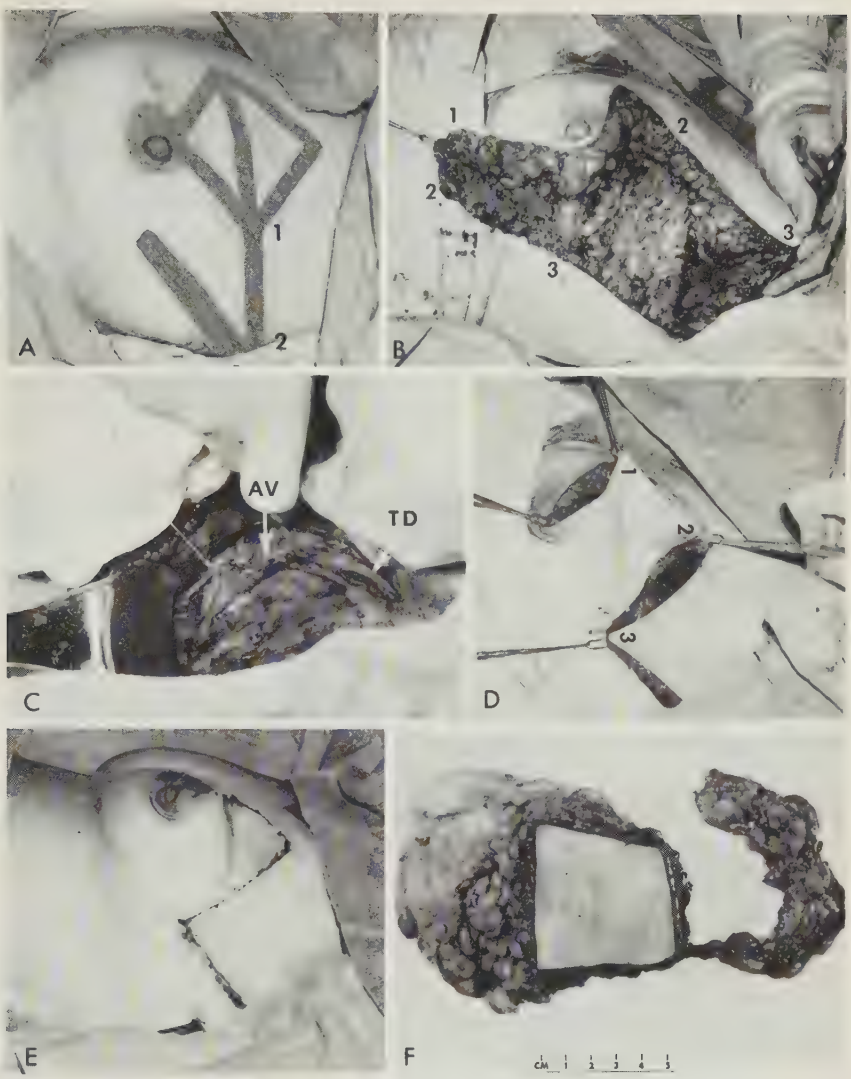

Figure 2. *A*, The patient is positioned prone on the operating table (head to the right, feet to the left). The left breast is exposed and the rhomboid marked for a lesion above the nipple. An extension into the axilla that will form the rhomboid flap has been included (1–2). *B*, The specimen has been excised and the rhomboid flap elevated (1–2). The future position of the rotated flap is shown (1, 2, 3). *C*, The dissected axilla showing axillary vein (AV), thoracodorsal vessels (TD), and medial anterior thoracic nerve (*thin arrow*) to the pectoralis minor muscle is shown. The retractor is obscuring the pectoralis muscles. *D*, The flap has been rotated into position as marked in B and the corresponding numbered points connected. *E*, Subcuticular closure and placement of Hemovac drains complete the operation. The upper portion healed without deformity. *F*, The excised specimen and incontinuity axillary dissection.

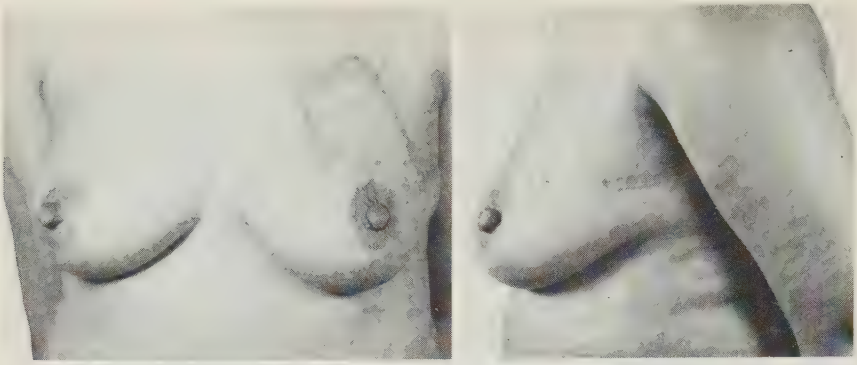

Figure 3. Rhomboid flap 3 months postoperatively. This patient had a lesion above and lateral to the nipple.

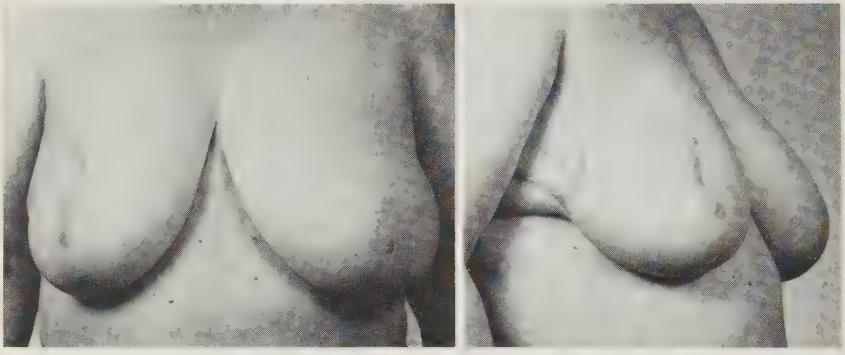

Figure 4. One year after partial mastectomy showing normal position of nipple with with minimal cosmetic deformity.

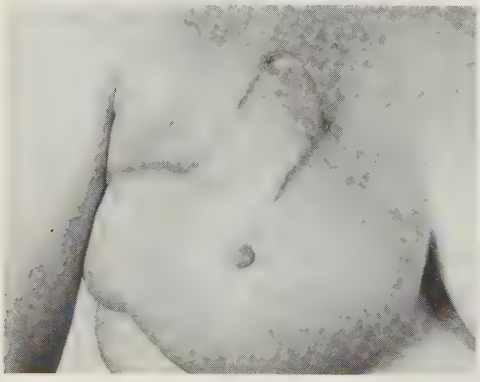

Figure 5. Early postoperative result two weeks after surgery.

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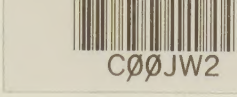

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